

PERSPECTIVE

# Generating real-world evidence in Alzheimer's disease: Considerations for establishing a core dataset

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## Abstract

Ongoing assessment of patients with Alzheimer's disease (AD) in postapproval studies is important for mapping disease progression and evaluating real-world treatment effectiveness and safety. However, interpreting outcomes in the real world is challenging owing to variation in data collected across centers and specialties and greater heterogeneity of patients compared with trial participants. Here, we share considerations for observational postapproval studies designed to collect harmonized longitudinal data from individuals with mild cognitive impairment or mild dementia stage of disease who receive therapies targeting the underlying pathological processes of AD in routine practice. This paper considers key study design parameters, including proposed aims and objectives, study populations, approaches to data

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collection, and measures of cognition, functional abilities, neuropsychiatric status, quality of life, health economics, safety, and drug utilization. Postapproval studies that capture these considerations will be important to provide standardized data on AD treatment effectiveness and safety in real-world settings.

#### KEYWORDS

Alzheimer's disease, core outcomes, data collection, population, real-world evidence, study aims

## 1 | BACKGROUND

Real-world evidence (RWE) generation is becoming increasingly important to clinicians, regulatory agencies, and professional societies to inform patient access and understand the effectiveness, safety, and appropriate use of therapeutic agents.<sup>1,2</sup> RWE can also be used to support regulatory decision making, and the US Food and Drug Administration (FDA) has issued guidance on how RWE can help inform drug approval and support postapproval study requirements;<sup>2-4</sup> real-world data collection as presented here is one type of Phase IV study in a clinical development program. Registries represent another approach to RWE generation and the prescribing information (PI) for ADUHELM (aducanumab-avwa) and for LEQEMBI (lecanemab-irnb) include reference to the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) as a voluntary patient registry that collects postmarketing information on treatments for Alzheimer's disease (AD).<sup>5-7</sup> Registries, such as the ALZ-NET registry, are data collection systems that capture a wide range of long-term outcome data.<sup>7,8</sup> In contrast, both registry studies, such as the Centers for Medicare & Medicaid Services (CMS) National Patient Registry study, and Phase IV observational studies investigate a specific research question that determines the parameters for data collection.<sup>8-10</sup> Both data from registries and postapproval studies can support regulatory decisions, but data from registries are generally more representative of the real-world population than postapproval studies and are preferable for assessing outcomes in subpopulations not included in Phase III trials; postapproval studies are preferred for assessing the clinical benefit and treatment strategies for novel drugs.<sup>11</sup> Since the US FDA accelerated approval of aducanumab and lecanemab (now traditionally approved) for the treatment of AD,<sup>5,6,12,13</sup> and with other anti-amyloid beta (A $\beta$ ) monoclonal antibodies in clinical development, the focus on RWE generation in AD has intensified, specifically to understand the long-term safety, effectiveness, and impact of anti-A $\beta$  monoclonal antibody treatment on patient-related and healthcare resource utilization outcomes. In addition, Appropriate Use Recommendations for both aducanumab and lecanemab have been recently published to guide the introduction of these therapies into clinical practice. These recommendations highlight the need for careful patient selection, including the presence of amyloid pathology; the exclusion of patients at high risk of developing amyloid-related imaging abnormalities (ARIA), such as those with cerebrovascular disease; recommendations for apolipoprotein E  $\epsilon$ 4 (APOE  $\epsilon$ 4) genotyping to assess ARIA risk;

and monitoring of asymptomatic ARIA using serial magnetic resonance imaging.<sup>14,15</sup>

Although randomized controlled trials (RCTs) are considered the gold-standard study design for evidence-based medicine, such studies have shortcomings in delivering generalizable information, as their methods can lack applicability in clinical practice.<sup>1,16,17</sup> RCTs are typically conducted in academic research settings or specialized trial sites by highly trained clinicians, where extrinsic factors are controlled, regimen adherence monitored, and interventions provided free of charge.<sup>17,18</sup> Participant selection can be narrow and homogeneous, which limits the generalizability of results; specific patient populations are not routinely included in RCTs, such as those of advanced age and/or with comorbidities.<sup>1,17,19</sup> African-American, Hispanic, and Latino individuals have been historically underrepresented in AD clinical trials despite having a greater risk of developing AD than White individuals, and research has found that many commonly used exclusion criteria (eg, history of cardiovascular disease or diabetes) in AD clinical trials disproportionately affect African American, Hispanic, and Latino individuals.<sup>20,21</sup> In addition, treatment and follow-up periods in RCTs are often short, potentially underestimating long-term benefits and/or safety signals.<sup>1,18</sup>

Real-world studies aim to produce findings that translate research to routine practice, maximize generalizability, explore key treatment-related factors driving clinical changes, and address considerations about the benefits, risks, and costs of an intervention.<sup>17</sup> RWE can be used to confirm the effectiveness and tolerability of treatments administered in routine conditions and support changes to labels (eg, new drug indications, new efficacy claims, addition of target populations, addition of administration information and patient-preference data, safety revisions, and additional information on health-related outcomes).<sup>22,23</sup> Owing to the longer duration, real-world data collection has the potential to demonstrate treatment effects that may not be realized until later in the disease course, beyond the period of observation in a clinical trial.<sup>1,18</sup> Furthermore, observational studies may provide opportunities to evaluate larger, more diverse, and less restricted populations compared with clinical trials, with exclusion criteria generally based on safety rather than selecting a homogeneous sample.<sup>1,17,22</sup>

Obtaining RWE requires efficient collection and robust analysis of data across disparate centers (eg, implementing common assessment tools, data quality systems, data exchange, data analysis, pooling of data, and strategies for interpretation across clinics).<sup>8</sup> Gathering data

and comparing outcomes of patients with confirmed AD in routine clinical practice can be challenging because cognitive, functional, neuropsychiatric, and quality of life (QoL) outcomes may not be measured consistently.<sup>22</sup> There is also a lack of consensus on optimal clinical assessments for longitudinal observational studies across the disease continuum from mild cognitive impairment to dementia, with global and regional variations in the instruments used at each disease stage, as well as a lack of large historical longitudinal datasets in patients with confirmed anti-A $\beta$  pathology. Finally, a variety of different healthcare professionals manage patients with AD, including advanced practice providers, family medicine practitioners, internal medicine specialists, neurologists, medical directors of residential facilities, and geriatric psychiatrists, adding further complexity to the issue. As a result of these various factors, RWE in AD can be difficult to interpret across cohorts and has poor transferability across healthcare systems.<sup>22</sup>

Given these challenges, a global International Collaboration for Real-world Evidence in Alzheimer's Disease (ICARE AD) program was created to provide a structure for collecting standardized longitudinal data from eligible patients treated with aducanumab-avwa in postapproval effectiveness studies. The program will no longer proceed owing to the national policy for coverage released by the CMS stating that anti-A $\beta$  monoclonal antibodies approved by the FDA through the accelerated approval pathway for AD will be covered by Medicare only for those enrolled in FDA- or National Institutes of Health-approved trials conducted under an investigational new drug application,<sup>24</sup> thereby limiting the use in clinical practice. Despite this, and in light of the CMS confirming that broader coverage is now available for lecanemab following traditional FDA approval,<sup>25</sup> the authors of this paper believe the approach to and rationale behind the design of this program offers valuable learnings for the field as robust RWE in AD remains an unmet need. In addition, this proposed program would augment the current CMS National Patient Registry study as it has a longer follow-up period (5 years vs 2 years) and collects additional data, such as QoL, lifestyle, and biomarker (for future analysis) data.<sup>9</sup> Data from this program would also complement data derived from the ALZ-NET registry, which is a general database that collects data from patients receiving any FDA-approved drug for AD, not specifically anti-A $\beta$  monoclonal antibodies, and does not collect QoL data.<sup>26</sup> Here we provide considerations for future studies assessing the use of anti-A $\beta$  monoclonal antibodies in a real-world setting, with a structure to utilize predefined, consistent assessments that will provide harmonized effectiveness and safety data and patient- and caregiver-reported outcomes.

## 2 | STUDY AIMS

Long-term clinical, QoL, and safety outcomes, including the incidence of ARIA, will be important to measure in future real-world AD studies. In addition, tools that provide insights into healthcare resource utilization and AD-related burden on informants/caregivers are valuable. Given an increasing emphasis placed on biomarkers, the collection of blood (plasma and serum) and optional cerebrospinal fluid for biobanking and potential genetic analysis is encouraged. Collectively, such

## RESEARCH IN CONTEXT

1. **Systematic review:** A literature review highlighted that obtaining and comparing real-world outcomes for patients with Alzheimer's disease (AD) is difficult owing to variation in data collected across centers.
2. **Interpretation:** There is a need to examine the long-term, real-world effectiveness and safety of therapies targeting known pathological processes of AD. We provide considerations for observational studies aiming to provide consistent longitudinal data from patients with AD, which will allow comparison of data across regions and transferability across healthcare systems to maximize data interpretability and inform best practices. Collecting data over a longer period and treating a more diverse population compared with registrational Phase III clinical trials will improve generalizability of findings.
3. **Future directions:** This paper aims to provide a framework for consistent data collection in real-world AD registries and studies as additional treatments enter clinical practice.

resources and data could serve as a platform for nested studies aiming to support progress in specific areas of interest related to digital assessments, magnetic resonance imaging and ARIA monitoring, and use of new blood-based biomarkers.

## 3 | STUDY POPULATIONS

The suggested eligibility criteria in Table 1 allow assessment of a larger and more heterogeneous patient population than is typically included in clinical trials, especially those who are historically underrepresented (eg, individuals who are ethnically/racially/geographically/socioeconomically diverse, have comorbid conditions or atypical disease, or are taking concomitant medications) to ensure that robust data are collected.<sup>1,17,19,22</sup> Expanded study eligibility can also enhance participant enrollment and retention, further driving patient diversity,<sup>27</sup> and ensure that study populations are representative of real-world patients.<sup>28,29</sup>

## 4 | STUDY OUTCOMES

Recommendations for primary, secondary, tertiary, and exploratory objectives and corresponding endpoints are described in Table 2.

The recommended assessment tools were selected in collaboration with an external steering committee of international clinical experts and patient advisory groups, following a review and analysis of instruments utilized in cohorts and registries. The criteria for

**TABLE 1** Suggested eligibility criteria.

| Standard inclusion criteria   |
|---|
| <ul style="list-style-type: none"> <li>• Patients aged <math>\geq 18</math> years</li> <li>• Diagnosis of AD (using investigator's choice of confirmatory assessments consistent with Appropriate Use Recommendations<sup>14</sup>)</li> <li>• Informed consent for data collection and able to complete QoL questionnaires</li> <li>• Requirement of an informant or caregiver who, in the investigator's opinion, has sufficient contact with the patient to provide accurate information about the patient's cognitive, functional, and behavioral status</li> <li>• Receiving anti-A<math>\beta</math> monoclonal antibody treatment</li> </ul> |
| Standard exclusion criteria   |
| <ul style="list-style-type: none"> <li>• Individuals unable to provide informed consent or to comply with study requirements, including blood (plasma and serum) collection and biobanking</li> <li>• Concurrently participating in any interventional clinical studies (participation in other noninterventional studies is permitted)</li> <li>• Treated with any investigational drug within 30 days or five half-lives (whichever is longer) prior to enrollment</li> <li>• Pregnant/breastfeeding</li> <li>• Contraindications to anti-A<math>\beta</math> monoclonal antibody treatment</li> </ul>  |

Abbreviations: A $\beta$ , amyloid beta; AD, Alzheimer's disease; QoL, quality of life.

instrument selection considered sensitivity to assess changes in cognition, functional abilities, and neuropsychiatric status in early-stage AD (mild cognitive impairment due to AD and mild AD dementia), which were identified through a comprehensive literature search of research analyzing test sensitivity. Further criteria included reliability, validity, ability to comprehensively assess AD clinical manifestations, and availability of existing data for untreated patients. Additionally, the measures need to be feasible for use in routine specialist practice, with appropriate formats for diverse populations, and easier and more rapid administration relative to clinical trial measures, facilitating efficient incorporation into the patient management workflow. Collection of descriptive information on the characteristics of patients with AD was recommended to gain a better understanding of AD, and the inclusion of QoL and health economic measures was intended to support measurement of the benefit/risk profile of future anti-A $\beta$  monoclonal antibodies entering clinical practice. Further details regarding the rationale for including specific assessment tools are provided in Table 3. An overview of the administration, validity, and limitations of the instruments is given in Data S1.

Data collected as part of a real-world study may be compared with matched external control groups (ie, from existing AD cohorts that represent comparators for natural disease progression, historical health insurance claims, or future registries) to characterize real-world, long-term changes in cognition, functional abilities, and neuropsychiatric status and evaluate any differences between treated and untreated patients and differences among treatments.<sup>30</sup> RWE may also be compared with data from placebo arms of clinical trials while acknowledging the limitations of existing AD trial cohorts (such as lack of diversity) when interpreting comparisons with these groups.<sup>19,21</sup> In this proposed study, including patients eligible for treatment but who decline this could be considered, but patients who decline treatment

may be difficult to follow up with, which could result in a misleading and partial dataset for such a comparator group.

In addition to measuring clinical outcomes, collecting blood and cerebrospinal fluid specimens is recommended for future biomarker and genetic studies in AD. Recent data have highlighted potential future applications of biomarkers, including as measures of disease progression, as prescreening tools for identifying patients with A $\beta$  pathology and other AD-related pathologies, and as screening tools for diagnosis and prognosis of patients to be included in clinical trials.<sup>31-39</sup> Biomarkers may also have a role in monitoring treatment response by demonstrating target engagement or as a surrogate of clinical benefit, as well as potentially predicting and monitoring side effects, such as ARIA due to vasogenic edema.<sup>32,39-42</sup> Biomarkers are now also being used to inform treatment decisions in clinical practice, with the aducanumab-awwa and lecanemab-irmb PIs stating that the presence of A $\beta$  pathology must be confirmed prior to initiating treatment.<sup>5,6</sup> However, there remain a lack of consensus on the choice of biomarker assays and cutoffs, an absence of prospectively collected data, and missing validation of key assay performance characteristics, especially in real-world populations.<sup>31,39,43</sup> Biobanking of longitudinal samples could enable biomarker substudies to be conducted and generate evidence for the validation, regulatory approval, and adoption of biomarkers as measures of brain AD pathology in patients with cognitive impairment, disease progression, and treatment response. Standardized procedures for sample collection and specimen storage need to be provided by the sponsors of the study.

## 5 | DATA COLLECTION

Study durations of at least 5 years are recommended to ensure adequate observation of longitudinal changes, given that A $\beta$  plaque levels have been found to continue to decline beyond 4 years of treatment with some anti-A $\beta$  monoclonal antibodies.<sup>5</sup>

To improve the diversity of enrolled participants, the FDA recommends accounting for logistical and patient-related factors that may limit participation in clinical studies, for example, reducing the burden of study participation by minimizing study visits and employing enrollment practices that enhance inclusiveness.<sup>29</sup> As such, study sites should be selected to represent a range of geographical locations and AD care settings (eg, academic centers, community memory clinics) with ethnically, racially, and socioeconomically diverse populations, as well as consideration of their ability to implement the core data elements. Data should typically be collected by trained site personnel as part of a structured interview (clinical assessment tools) or collected prospectively as part of an unstructured interview (medical history). For a real-world study of this duration, it is recommended that data be gathered during routine visits conducted within the context of standard of care, with intervals for data collection of approximately 6 to 12 months. Self-administered cognitive assessments, such as the Quick Dementia Rating System Patient Version (QDRS-PV), which can be completed prior to the physician visit, may reduce study site burden, but they can be associated with some challenges, including reduced response validity (compliance, effort, motivation) because of a lack of

**TABLE 2** Proposed study objectives and endpoints.

| Primary objective  | Primary endpoints   |
|--|---|
| Evaluate long-term AD progression in treated patients with early-stage AD (MCI due to AD or mild AD dementia) as determined by cognitive, functional, and neuropsychiatric measures and to describe the QoL, caregiver burden, and HCRU longitudinally | <p>Changes in cognition, functional abilities, and neuropsychiatric status as measured during routine visits from baseline through end of study by:</p> <ul style="list-style-type: none"> <li>• QDRS-IV</li> <li>• QDRS-PV</li> <li>• A-IADL-Q-SV</li> <li>• FAQ</li> <li>• MoCA (version 8.1)</li> <li>• NPI-Q</li> <li>• GDS-SF</li> </ul> <p>Changes in QoL, caregiver burden, and HCRU captured during routine visits from baseline through end of study by:</p> <ul style="list-style-type: none"> <li>• 13-item QoL-AD</li> <li>• ZBI (22 items)</li> <li>• SF-12 (version 2)</li> <li>• RUD Lite</li> <li>• PGI-S</li> <li>• PGI-C</li> </ul> |
| Secondary objectives   | Secondary endpoints   |
| Evaluate incidence of AEs, including SAEs, in treated patients   | <ul style="list-style-type: none"> <li>• Incidence of AEs including SAEs in treated patients</li> </ul>   |
| Assess incidence of treatment-associated ARIA in real-world practice per label recommendation for safety monitoring<br>Estimate incidence of symptomatic ARIA in real-world clinical practice  | <ul style="list-style-type: none"> <li>• Incidence of ARIA-E and ARIA-H (micro-hemorrhage and superficial siderosis) in treated patients</li> <li>• Incidence of symptomatic ARIA and type of symptoms of ARIA (AEs deemed related to ARIA as determined by investigator)</li> </ul>  |
| Compare incidence of SAEs in patients with and without ARIA  | <ul style="list-style-type: none"> <li>• Incidence and type of SAEs in treated patients with and without ARIA</li> </ul>  |
| Evaluate incidence of brain hemorrhage-treated patients in real-world clinical practice  | <ul style="list-style-type: none"> <li>• Incidence and clinical symptoms of brain hemorrhages</li> </ul>  |
| Obtain descriptive statistics on characteristics of treatment population and drug utilization  | <ul style="list-style-type: none"> <li>• Descriptive statistics on patient characteristics, including age, sex, geography, comorbidities, lifestyle, concomitant AD and other medications, and stage and severity of AD at drug initiation (including any off-label use)</li> <li>• Descriptive statistics on frequency of prescription; descriptive statistics on ARIA-E monitoring patterns in relation to approved label</li> <li>• Descriptive statistics on treatment duration and incidence of discontinuation</li> </ul>   |
| Tertiary objective   | Tertiary endpoint   |
| Generate longitudinal biobank for future AD plasma or serum biomarker research   | <ul style="list-style-type: none"> <li>• Blood samples (plasma and serum) throughout duration of patient participation in study at baseline and at approximately Months 6, 12, 24, 36, 48, and 60</li> </ul>  |
| Exploratory objectives (where available)   | Exploratory endpoints   |
| Evaluate long-term treatment effects on biomarkers related to AD development or progression  | <ul style="list-style-type: none"> <li>• Optional CSF sample with biomarker data: change in levels of fluid biomarkers related to disease, which may include, but are not limited to, amyloid and tau proteins</li> </ul>   |
| Collect samples for future genetic and biomarker research  | <ul style="list-style-type: none"> <li>• Optional, one-time collection of blood for future genetic and biomarker research</li> </ul>  |

Abbreviations: AD, Alzheimer's disease; AE, adverse event; A-IADL-Q-SV, Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities due to vasogenic edema; ARIA-H, amyloid-related imaging abnormalities due to micro-hemorrhages, macro-hemorrhages; CSF, cerebrospinal fluid; FAQ, Functional Activities Questionnaire; GDS-SF, Geriatric Depression Scale Short Form; HCRU, healthcare resource utilization; MoCA, Montreal Cognitive Assessment; NPI-Q, Neuropsychiatric Inventory Questionnaire; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; QDRS-IV, Quick Dementia Rating System Informant Version; QDRS-PV, Quick Dementia Rating System Patient Version; QoL, quality of life; QoL-AD, Quality of Life in Alzheimer's Disease; RUD, Resource Utilization in Dementia; SAE, serious adverse event; SF-12, 12-item Short Form Survey; ZBI, Zarit Burden Interview.

**TABLE 3** Rationale for suggested assessment tools.

| Assessment tool   | Rationale for inclusion   |
|---|---|
| Montreal Cognitive Assessment (MoCA)  | <ul style="list-style-type: none"> <li>Brief and easy-to-administer screening tool assessing cognition that is available in multiple languages<sup>44,45</sup></li> <li>Allows for simple adjustment of education level (one point added to total score for patients with <math>\leq 12</math> years of education)<sup>44</sup></li> <li>Can be administered remotely by trained clinicians to increase access and ease of use (audiovisual conferencing and abbreviated telephone versions are available)<sup>46</sup></li> <li>Involves more words, potentially fewer learning trials, and a longer delay before recall compared with MMSE<sup>44</sup></li> <li>Better assesses cognitive domains of executive functions and working memory, which are important domains to evaluate, given that they are often impaired in early-stage AD,<sup>44</sup> compared with MMSE</li> </ul>   |
| Quick Dementia Rating System Informant Version/Patient Version (QDRS-IV/PV)                 | <ul style="list-style-type: none"> <li>Rapid informant- and patient-based screening tools assessing cognition<sup>47,48</sup></li> <li>Able to differentiate individuals with and without cognitive impairment and provide accurate dementia staging<sup>47,48</sup></li> <li>No extensive training or clinician input required and can be completed prior to a physician visit<sup>47,48</sup></li> <li>The patient version can be used when caregivers are not available<sup>48</sup></li> <li>Strongly correlated with gold-standard evaluations, such as CDR-G and CDR-SB, neuropsychological testing, and other validated measures of dementia severity, behavior, and caregiver concerns<sup>47,48</sup></li> <li>Validity has been demonstrated in research and community real-world settings and demonstrates good correlation with AD biomarkers<sup>47,49</sup></li> </ul>  |
| Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version (A-IADL-Q-SV) | <ul style="list-style-type: none"> <li>A computerized questionnaire assessing functional abilities, specifically day-to-day problems caused by cognitive difficulties<sup>50</sup></li> <li>Comparable psychometric properties with A-IADL-Q, but shorter length makes it more suitable for everyday clinical practice<sup>50</sup></li> <li>Developed with input from patients, caregivers, and healthcare providers, supporting content validity<sup>51</sup></li> <li>High construct validity, supported by concordance with MMSE<sup>50</sup> and limited correlation with age, sex, and education<sup>52</sup></li> <li>High test-retest reliability, very high internal consistency, and unidimensional factor structure<sup>50</sup></li> <li>Able to differentiate between various diagnostic groups with respect to IADL impairment<sup>50</sup></li> <li>High sensitivity to change compared with traditional IADL outcomes<sup>53</sup></li> <li>Related to AD-specific neurodegeneration<sup>54</sup></li> <li>Completed by study partner, with a self-report version also available<sup>55</sup></li> <li>Extensive cross-cultural validation supports use of different languages and culturally adapted versions<sup>56</sup></li> <li>Cut-off values available for clinically meaningful decline, as determined across stages of AD in mixed-methods study<sup>57</sup></li> </ul> |
| Neuropsychiatric Inventory Questionnaire (NPI-Q)  | <ul style="list-style-type: none"> <li>A short screening questionnaire to assess neuropsychiatric symptoms and the associated impact on caregivers<sup>58,59</sup></li> <li>A self-administered questionnaire completed by informants about patients under their care, which provides useful information when working with patients' caregivers and families<sup>58,59</sup></li> <li>Most caregivers complete questionnaire in less than 5 min, meaning it is feasible to implement in routine clinical practice<sup>58,59</sup></li> <li>Adequate test-retest reliability<sup>58</sup></li> <li>The total symptom score is robustly correlated with the NPI in populations with a range of dementia severities<sup>58</sup></li> </ul>  |
| Quality of Life in Alzheimer's Disease (QoL-AD)   | <ul style="list-style-type: none"> <li>A brief, easily administered assessment of QoL in AD<sup>60</sup></li> <li>Rates patient's QoL from both patient and caregiver via interview and self-completed questionnaire, respectively. The two scores can be considered individually, or a composite score can be calculated<sup>60,61</sup></li> <li>Uses simple/straightforward language and responses to optimize use in patients with cognitive impairment<sup>60,61</sup></li> <li>Reliably and validly rates QoL of a patient with mild to moderate dementia<sup>60,61</sup></li> </ul>  |
| 12-item Short-Form Survey (SF-12)   | <ul style="list-style-type: none"> <li>A widely used instrument for assessing self-reported health-related QoL<sup>62,63</sup></li> <li>Takes less than 2 min to complete, making it a useful tool for those with limited attention spans<sup>62</sup></li> <li>Includes the same eight health domains as the SF-36 with substantially fewer questions<sup>62,63</sup></li> <li>A high degree of correlation with SF-36<sup>62</sup></li> <li>Proven to be reliable and valid in clinical and population-based applications<sup>62</sup></li> </ul>   |

(Continues)

**TABLE 3** (Continued)

| Assessment tool  | Rationale for inclusion  |
|--|--|
| Patient Global Impression of Severity/Change (PGI-S/C) | <ul style="list-style-type: none"> <li>• Quick assessments collecting data on patients' perceptions of their condition<sup>64</sup></li> <li>• Simple to use, scores are easily calculated, and no training is required for their use<sup>64</sup></li> <li>• Correlates moderately to highly with other patient-reported measures, including across variations in ethnicity<sup>65</sup></li> </ul> |
| Zarit Burden Interview (ZBI)                           | <ul style="list-style-type: none"> <li>• A commonly used instrument providing a comprehensive assessment of objective and subjective burden for caregivers of patients with dementia<sup>66</sup></li> <li>• Validated in many culturally and ethnically diverse populations<sup>66</sup></li> <li>• Highly correlated with other standardized instruments<sup>66</sup></li> </ul>                   |
| Resource Utilization in Dementia (RUD) Lite Scale      | <ul style="list-style-type: none"> <li>• Assesses both formal and informal resource use, meaning it is possible to calculate costs from a societal perspective<sup>67</sup></li> <li>• Demonstrated to be a valid measure of the amount of time provided by caregivers to patients with dementia<sup>67</sup></li> </ul>   |

Abbreviations: AD, Alzheimer's disease; A-IADL-Q, Amsterdam Instrumental Activities of Daily Living Questionnaire; A-IADL-Q-SV, Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version; CDR-G, Clinical Dementia Rating Global Score; CDR-SB, Clinical Dementia Rating Scale-Sum of Boxes; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; NPI-Q, Neuropsychiatric Inventory Questionnaire; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; QDRS-IV, Quick Dementia Rating System Informant Version; QDRS-PV, Quick Dementia Rating System Patient Version; QoL, quality of life; QOL-AD, Quality of Life in Alzheimer's Disease; RUD, Resource Utilization in Dementia; SF-12, 12-item Short-Form Survey; SF-36, 36-item Short Form Survey; ZBI, Zarit Burden Interview.

monitoring, loss of qualitative data obtained from conventional evaluations, risk of interruptions, and lack of support for the patient if they are struggling to complete the task or experience technological problems.<sup>48,68</sup>

An overview of the recommended schedule of data collection is shown in Figure 1. A detailed schedule of assessments is listed in Table S1; core data elements are noted to ensure consistency of clinical assessments and demographics collection, with data that may not be collected in routine practice considered optional to minimize study site burden and maximize real-world relevance.

## 6 | LIMITATIONS OF PROPOSED REAL-WORLD STUDIES

The potential limitations of a real-world study are that some components may not be typical of clinical practice, namely, trained raters, extensive data and biomarker collection, and the requirement to enter results into a database, all of which may result in greater recruitment from research centers than other clinical settings. Moreover, the practicalities of implementing such a core dataset may be challenging, owing to regional variations in resource availability, differences in clinician specialty and training, the requirement for translation and validation of assessment tools, and reimbursement of AD biomarker investigations. The process of recruitment and consent in such a study may also introduce bias based on comorbidities, language, socioeconomic status, and ethnicity.

## 7 | CONCLUSION

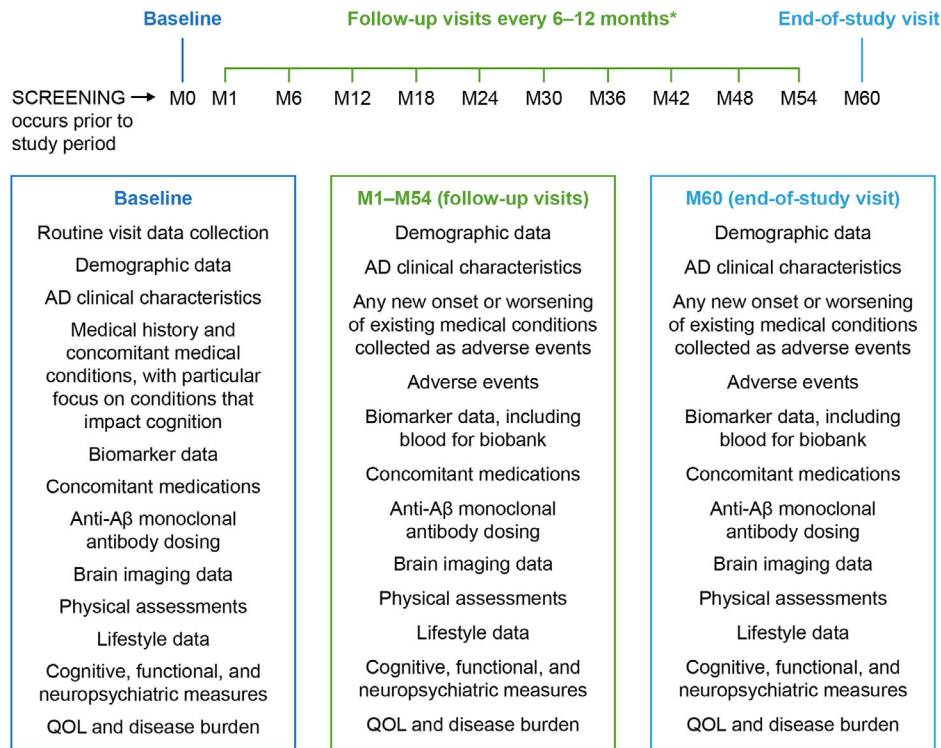
An important objective of the current AD treatment landscape is to monitor patient outcomes and evaluate disease progression.

Real-world studies can be compromised by inconsistent collection of data and use of nonstandardized endpoints, which can limit the generalizability of results. As summarized in Table 4, these considerations

**TABLE 4** Summary of proposed RWE benefits.

| Limitations of RCTs                          | Benefits of proposed RWE  |
|--|---|
| Population diversity                         | Broader eligibility criteria; inclusion of community healthcare settings; minimal trial participant burden; inclusion of patients underrepresented in clinical trials                             |
| Study duration                               | Longer period of observation to evaluate longitudinal changes   |
| Generalizability and transferability of data | Robust framework for collecting harmonized data, with core elements across all participating centers for consistent collection and interpretation; consensus on optimal clinical assessment tools |
| Selectivity and sensitivity of instruments   | Range of well-validated measures of cognition, functional abilities, neuropsychiatric status, quality of life, health economics, safety, and drug utilization                                     |
| Healthcare-related burden evaluation         | Inclusion of patient- and caregiver-reported outcomes, QoL, and HCRU measures in real-world clinical context  |
| Real-world applicability                     | Clinical assessments tailored to standard-of-care clinical practice in varied healthcare settings   |
| Data interpretation                          | Comparison with matched natural history cohorts, health insurance claims, or registries to evaluate differences between treated and untreated patients  |

Abbreviations: HCRU, healthcare resource utilization; QoL, quality of life; RCT, randomized controlled trial; RWE, real-world evidence.



**FIGURE 1** Schedule of data collection. \*Study information may be collected at any routine clinical visits scheduled per local standard of care. Data from radiological assessments of MRI scans will be collected at each MRI visit. It is expected that after a patient reaches target dosing, information on each patient will be collected at the physician's discretion or as part of routine clinical practice, anticipated to be approximately every 6 to 12 months. AD, Alzheimer's disease; M, month; MRI, magnetic resonance imaging; QoL, quality of life.

for collecting RWE in AD, adapted from the now closed ICARE AD program, may address some of the limitations of RCTs and help ensure consistent, longitudinal data collection across the AD continuum in routine practice to allow for transferability of data across healthcare systems.

#### AUTHOR CONTRIBUTIONS

All authors participated in the review of the literature and the drafting and review of the manuscript. All authors read and approved the final manuscript.

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#### CONFLICT OF INTEREST STATEMENT

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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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