Alzheimer's Network for Treatment and Diagnostics (ALZ-NET)

Sponsored by: Alzheimer's Association
Managed by: American College of Radiology

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Protocol Number: 4709 **NCT#:** NCT06170268

Protocol Version: 4.0 **Protocol Date:** January 10, 2025

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GLOSSARY

Abbreviation	Definition
ACR®	American College of Radiology®
ACRP	Association of Clinical Research Professionals
AD	Alzheimer's Disease
ADRD	Alzheimer's Disease Related Dementia
AE	Adverse Event
ALZ-NET	Alzheimer's Network for Treatment and Diagnostics
API	Application Programming Interface
APP	Advance Practice Providers
ARIA	Amyloid Related Imaging Abnormalities
ASNR	American Society of Neuroradiology
AUC	Appropriate Use Criteria
CED	Coverage with Evidence Development
CITI	Collaborative Institutional Training Initiative
CMS	Centers for Medicare & Medicaid Services
Co-PI	Co-Principal Investigator
CRF	Case Report Form
CRI	Center for Research and Innovation
CSF	Cerebrospinal Fluid
CSS	Center for Statistical Sciences
DNA	Deoxyribonucleic acid
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
HHS	Health and Human Services
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDEAS	Imaging Dementia-Evidence for Amyloid Scanning
IRB	Institutional Review Board
LAR	Legally Authorized Representative
MCI	Mild Cognitive Impairment
NIA	National Institute of Aging
NOPR	National Oncologic PET Registry
NPI	National Provider Identifier
PET	Positron Emission Tomography
PHI	Protected Health Information
SAE	Serious Adverse Event
sFTP	Secure File Transfer Protocol
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SOC	Standard of Care
U.S.	United States

1.0 ABSTRACT

There are over 120 therapies being tested in clinical trials for Alzheimer's disease (AD) today[1]. With therapies undergoing regulatory review and a growing drug development pipeline, the field is entering a new era of molecular-specific therapies. A national registry represents an opportunity to evaluate the longitudinal outcomes of patients being evaluated for and treated with novel FDA-approved AD therapy in real-world settings, to inform clinical practice.

The Alzheimer's Association, the American College of Radiology, the American Society of Neuroradiology, and the Department of Biostatistics, Brown University School of Public Health along with other clinical research and imaging experts, launched the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET). ALZ-NET builds on expertise from successful networks in other therapeutic areas and from the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) and New IDEAS studies which demonstrated that large-scale, real-world data collection in dementia practice is feasible for addressing critical research questions. Networks of dementia practices and imaging facilities provide the foundation for ALZ-NET. Data collection and sharing is fully compliant with human patient protections, privacy and patient/provider autonomy. This protocol for a voluntary provider-enrolled patient registry, collecting retrospective and prospective data, will be conducted according to International Conference on Harmonization Good Clinical Practice Guidelines, applicable government regulations (e.g., Title 45, Part 46 Code of Federal Regulations), standards of scientific integrity (i.e. ICMJE and Agency for Healthcare Research and Quality), and the American College of Radiology (ACR) research policies and procedures.

ALZ-NET will collect longitudinal clinical and safety data for enrolled patients being evaluated for and treated with novel FDA-approved AD therapies and will track patient long-term health outcomes (clinical response, health outcomes, and safety), associated with use in real-world settings. ALZ-NET aims to assess the clinical course of individuals from a variety of backgrounds and communities, to achieve representativeness beyond the populations historically enrolled in clinical trials.

Objectives of ALZ-NET:

- Develop a multisite network for enrolling providers and collection of patient data.
- Collect baseline and longitudinal patient data, including measures of cognition, function, and long-term safety.
- Collect and archive diagnostic, genetic, and fluid biomarkers.
- Track health outcomes and resource utilization through existing databases.
- Share de-identified data, images, and biosamples with the research community and other partners.

ALZ-NET will establish a national, longitudinal registry with an expandable platform, allowing for the collection of real-world data from enrolled patients being evaluated for, or treated with, novel FDA-approved AD therapies. ALZ-NET will be a resource for evidence gathering, information sharing and education across clinical and research communities, encouraging innovative, inclusive research and supporting opportunities to improve care.

2.0 INTRODUCTION

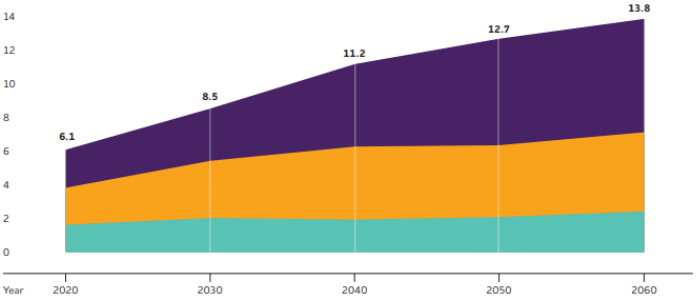
Today, nearly 7 million Americans are living with AD or a related dementia (ADRD). Seventy-three percent of these individuals are age 75 or older. As an increasing portion of the U.S. population continues to reach age 65 and older, the number of Americans with AD/ADRD will grow. Individuals who reach age 65 and beyond are in the age range at greatest risk of AD and other dementia.[2,3,4] The oldest members of the baby-boom generation (Americans born between 1946 and 1964) turned age 75 in 2021.

The costs of health care and long-term care for individuals with AD or other dementia are substantial; total payments in 2024 (in 2024 dollars) for all individuals with Alzheimer's or other dementias are estimated at $360 billion, not including the value of unpaid caregiving by family or others.[2]

AD is the most common cause of dementia, accounting for an estimated 60% to 80% of cases.[2] Difficulty remembering recent conversations, names or events is often an early clinical symptom of AD; apathy and depression are also sometimes seen as early symptoms.[2] Later symptoms include impaired communication, disorientation, confusion, poor judgment, behavioral changes and, ultimately, difficulty speaking, swallowing and walking.

FIGURE 5

Projected Number of People Age 65 and Older (Total and by Age) in the U.S. Population with Alzheimer's Dementia, 2020 to 2060



Created from data from Rajan et al.[A1,216]

Pathologically, AD is defined by the accumulation of the protein fragment beta-amyloid (plaques) outside neurons in the brain and twisted strands of the protein tau (tangles) inside neurons. These changes are accompanied by the death of neurons and damage to brain tissue. AD is a slowly progressive and ultimately fatal brain disease that begins many years before symptoms emerge.[2]

AD occurs across a continuum with three broad phases: preclinical Alzheimer's disease, mild cognitive impairment (MCI) due to Alzheimer's disease and dementia due to Alzheimer's disease.[5,6,7] Preclinical AD describes asymptomatic individuals with AD-related brain changes and is a research construct, while MCI due to AD and dementia due to AD are used clinically to describe specific stages of the disease continuum. Patients with MCI show evidence of decline in cognition from baseline and perform in the impaired range on objective cognitive tests but are still independent in performing daily life activities.

Patients with dementia show cognitive decline that renders them no longer independent in daily function. Dementia due to AD is further broken down into the stages of mild, moderate, and severe, which reflect the degree to which symptoms interfere with one's ability to carry out everyday activities. Numerous clinical studies - both interventional and longitudinal - suggest underlying biological disease occurs 10 to 20 years prior to the onset of clinical symptoms. As the disease progresses, cognitive and functional impairments and behavioral changes become more pronounced.

AD is a complex disease process involving a number of biological mechanisms that interplay with each other - including beta-amyloid plaques, tau tangles, metabolic mechanisms, loss of homeostasis of the cell, change synaptic plasticity and overall health, dysregulation of immune function and inflammation as well as many other intersecting biological contributors. The presence of AD pathophysiology (i.e., amyloid plaques and tau tangles) in patients with MCI or dementia can be established using biomarkers, including established cerebrospinal fluid (CSF) assays and positron emission tomography (PET) radiotracers and emerging plasma assays for amyloid-β and phosphorylated tau. There are a number of therapies being explored to target specific aspects of these pathways. Developing therapies also explore

combination approaches of these biological underpinnings in the context of behavioral intervention based on the timeline of when the biology may be most affected. More recently, with increased understanding of the underlying disease process preceding the symptom onset by decades, the scientific community has also focused on developing treatments for individuals in the earlier stages of the AD continuum.

Between 2021-2024, the amyloid-targeting therapies Aduhelm® (aducanumab), Leqembi® (lecanemab) and Kisunla™ (donanemab) received approval as treatments for AD from the U.S. Food and Drug Administration (FDA). These are the first approved treatments that slow disease progression by targeting the underlying biology of the disease process for individuals with MCI or mild dementia due to AD. Rexulti® (brexpiprazole) was approved in 2023 for the treatment of agitation associated with dementia due to Alzheimer's disease. With additional treatments undergoing regulatory review and a growing drug development pipeline, the field is entering a new era of molecular-specific therapies. A national voluntary provider-enrolled patient registry designed with an expandable platform to grow with scientific and medical advancements will be needed as new treatments and diagnostics are approved and implemented in care. This platform is necessary to track the long-term health outcomes in a real-world setting to inform clinical practice and support innovative research.

The Alzheimer's Association, the American College of Radiology (ACR), the American Society of Neuroradiology (ASNR), and the Department of Biostatistics, Brown University School of Public Health, along with other clinical research and imaging experts, will partner to implement ALZ-NET. The Alzheimer's Association, ACR, and Brown University have significant experience in developing and conducting real-world evidence-based studies as exemplified by the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study which evaluated the impact of beta-amyloid (Aβ) PET on patient-oriented outcomes in Medicare beneficiaries aged ≥ 65 with Mild Cognitive Impairment (MCI) or atypical dementia meeting Appropriate Use Criteria (AUC) for amyloid imaging, as well as the recently concluded New IDEAS Study.

Overall, ALZ-NET will build on expertise from successful networks developed for other neurologic and systemic diseases and leverage the groundwork from the IDEAS and New IDEAS studies. These studies have demonstrated that large-scale, real-world data collection in dementia practice is feasible for addressing critical research and treatment questions regarding dementia care. Networks of dementia clinics and imaging facilities will provide the foundation of ALZ-NET as it expands over time to include a variety of clinical practices to address gaps in knowledge that are highly relevant to improving treatment of AD in real-world clinical practice.

3.0 SCOPE OF ALZ-NET

ALZ-NET will collect longitudinal clinical, imaging, and safety data for enrolled patients being evaluated for, and treated with, novel FDA-approved AD therapies and will track patient long-term health outcomes (effectiveness and safety), associated with the use of these therapies in real-world settings. ALZ-NET aims to assess the clinical course of people from a variety of backgrounds and communities in order to achieve representativeness beyond the populations historically enrolled in clinical trials. ALZ-NET will establish a national, longitudinal network with an expandable platform, allowing for the collection of real-world data from enrolled patients being evaluated for or receiving novel FDA-approved AD therapies. ALZ-NET also aims to harmonize with international efforts associated with data collection from patient populations across a variety of countries and health systems. ALZ-NET will be a resource for evidence gathering, information sharing, and education across both national and international clinical and research communities, encouraging innovative, inclusive research and supporting opportunities to improve care.

A major limitation of current and past interventional pharmaceutical clinical trials is a lack of racial and ethnic representation within the cohorts. This likely reflects discrepancies in access to specialist care, as

well as the need for tailored approaches to successfully recruit representative populations into research studies. In 35 years, one-third of the U.S. population over the age of 85 will be Latino/Hispanic, Black/African-American or other ethnoracial minority; if current trends persist, >50% of these individuals will suffer from dementia.[8] Based on clinical trials, little is known about treatment performance in these under-represented populations, even though altogether these groups will comprise the majority of the elderly population by 2050. A comprehensive, multi-disciplinary approach is needed to effectively recruit these under-served populations into tertiary care and to follow their diagnostic and treatment outcomes.

To achieve its aims, ALZ-NET will utilize, amongst additional strategies, the dementia practice networks developed through the IDEAS and New IDEAS studies.

ALZ-NET will align with the following objectives:

- Develop a multisite network for enrolling providers and collection of patient data.
- Collect baseline and longitudinal patient data, including measures of cognition, function, and long-term safety.
- Collect and archive diagnostic, neuroimaging, genetic and fluid biomarkers.
- Track health outcomes and resource utilization through existing databases.
- Share de-identified data, images and biosamples with research community and other partners.

ALZ-NET is designed to grow with scientific and medical advancements. As new drugs are approved and implemented in care, these will also be captured by ALZ-NET to assess the benefits that people from all backgrounds and communities derive from newly approved and future treatments in the real world i.e., outside of narrowly constrained clinical trials. It will collect longitudinal data through site-submitted case report forms and payer claims from individuals who are being approved for or treated with novel FDA-approved AD therapeutics, based on their label designation. Additional objectives of ALZ-NET are to establish a biorepository of plasma and DNA samples and to archive brain images from patients who consent to these optional elements.

In addition to the aims and objectives outlined within this protocol, ALZ-NET will serve as a backbone registry and platform for the collection of regulatory-grade data and collaboration with affiliated studies. Affiliated studies are thoroughly reviewed by the ALZ-NET Steering Committee before receiving affiliation approval. ALZ-NET will allow for seamless co-enrollment of patients being evaluated for or those receiving a novel FDA-approved treatment for AD. This collaboration structure is designed to reduce the operational burden of participating sites and patients. Patients will be required to provide separate informed consent authorization for any affiliated studies they choose to also participate in. A separate registration process will also occur; however, any overlapping data elements being collected by ALZ-NET and an affiliated study will only require data entry into one database. All site staff and patients should refer to applicable affiliated study protocols and informed consent forms for additional information. Approved affiliated studies will be listed on the ALZ-NET website (www.alz-net.org).

4.0 RATIONALE FOR ALZ-NET

There is an urgent need to provide a cohesive strategy for detection, diagnosis, treatment and evidence-based care of all individuals and their families affected by AD as well as approaches to support data and evidence generation from real-world settings to accelerate research advances for both treatments and diagnostics. An integrated approach to high-quality data collection from a variety of clinical practices, health records and a broad patient population will be necessary to fill gaps in knowledge regarding long term health outcomes for individuals evaluated and treated with novel FDA-approved AD therapies. Frontline clinicians will need a supportive infrastructure that creates an environment of clinical and system readiness and encourages patient participation. Finally, optimizing a real-world evidence platform will require a transparent approach that allows for responsible data sharing and learnings with of the research community and other partners.

The field is now entering a new phase of research, treatment and care. Recently, the FDA approved the first novel treatments aimed at the underlying biology of AD and additional therapies are currently entering regulatory review. Notably, the prescribing information for the new AD therapeutics encourages clinicians and patients to participate in ALZ-NET.[9,10] ALZ-NET is also included in the FDA's post marketing requirements for two recently approved amyloid-targeting Alzheimer's therapies. ALZ-NET participation is encouraged by a variety of United States commercial payer medical policies. Furthermore, ALZ-NET is approved by the Centers for Medicare and Medicaid Services (CMS) as a Coverage with Evidence Development (CED) study and can be used as a pathway to Medicare coverage for anti-amyloid Alzheimer's therapies that have received traditional FDA approval. These reasons, along with other diverse experimental treatment approaches in the drug development pipeline, make a national provider-enrolled patient registry platform essential for researchers, clinicians and people living with the disease.

ALZ-NET will enable the collection of data regarding the long-term clinical outcomes, both cognitive and functional, as well as health outcomes and resource utilization of individuals with AD in real world clinical settings being evaluated for and treated with novel FDA-approved AD therapies. Furthermore, it will assess the long-term safety of novel FDA-approved AD therapies by capturing adverse events (AEs) including serious adverse events (SAEs), and any events that may be specific to each novel FDA-approved AD treatment over the long-term (e.g., in the case of monoclonal antibody anti-amyloid treatments, the incidence and management of amyloid related imaging abnormalities (ARIA)). Finally, to identify possible biomarkers or genes key to the AD process, optional blood (plasma and serum) and CSF collection for biobanking will provide specimens for genetic analysis and future biomarker studies. Refer to section 15.0 for additional information on biosample collection.

Creation of a national voluntary provider-enrolled patient network for novel FDA-approved treatments for AD, and for the associated diagnostic tests and biomarkers, is meant to swiftly advance the science, as the pipeline is growing, including several more disease-modifying therapies that may be approved in the next two to three years. Similar successful registries in heart disease and cancer have enabled collaborators to track the long-term performance of therapies using a large, real-world evidence dataset.

5.0 ALZ-NET SPECIFIC AIMS

The ALZ-NET protocol addresses key scientific knowledge gaps, and is designed to grow with scientific and medical advancements, seeking to facilitate an increased understanding of treatment use in real world practice, through the following Specific Aims:

AIM 1: Establish the necessary network infrastructure:

- Develop a database to gather regulatory grade, longitudinal data from patients being evaluated for or treated with novel FDA-approved therapies for AD in real-world clinical practice.
- Establish an image repository to collect and archive diagnostic and safety neuroimaging studies.
- Establish a biorepository for specimens and systems to distribute specimens as research projects are approved.

AIM 2: The registry will collect data to evaluate long term safety, clinical use and outcomes:

- Characterize the patient population and clinician prescribing patterns.
- Track baseline and longitudinal safety, cognitive, and functional trajectories.
- Assess patient management including initiation and duration of treatment.
- Evaluate longitudinal safety and tolerability.

AIM 3: The registry will develop mechanisms to co-enroll patients in affiliated trials.

AIM 4: Merge and compare ALZ-NET data with existing databases to further understand patient outcomes and resource utilization.

AIM 5: Establish and implement infrastructure for sharing of de-identified data, images and biosamples.

6.0 ALZ-NET LEADERSHIP AND ORGANIZATIONAL STRUCTURE

The ALZ-NET organizational structure has been modeled after other successful studies of this type and attempts to provide the optimal balance between direct oversight and broad engagement. The combination of the ALZ-NET Project Team, Operations Center, Advisors and Partnering Organizations creates an effective multidisciplinary governing team (with associated workgroups and subcommittees), that will promote large-scale access to ALZ-NET while ensuring maximum data integrity.

6.1 ALZ-NET Project Team

ALZ-NET is led by a team of co-principal investigators (co-PIs) that have extensive experience in clinical research of Alzheimer's disease and related dementia (ADRD). The co-PIs have assembled a multidisciplinary group of respected and published individuals to form a Project Team. This Project Team serves to provide expertise and guidance in their respected domain as it pertains to dementia care and/or clinical research. Under the direction of the co-PIs, ALZ-NET is ideally suited for the ongoing development, conduct and output of ALZ-NET.

The ALZ-NET Project Team will convene on average monthly and will support the scientific vision of ALZ-NET by monitoring progress against established timelines, evaluating scientific program initiatives, and ensuring publication and dissemination of data. A detailed membership list for the ALZ-NET Project Team will be posted and maintained on the ALZ-NET website.

Workgroups and subcommittees will be created under the Project Team as needed to perform additional functional roles. Established subcommittees include, but are not limited to, a Data Access and/or Management Committee, a Communications and Recruitment Committee, an Imaging Committee, and an Education Committee.

6.2 ALZ-NET Partner Organizations

American College of Radiology (ACR)

The American College of Radiology® (ACR®) is a professional medical society dedicated to serving patients and society by empowering radiology professionals to advance the practice, science and professions of radiological care. The ACR will serve as the clinical research organization and operations center. The ACR will also provide the ALZ-NET Investigators with expertise and guidance on imaging related aspects of ALZ-NET. Imaging expertise will be provided through leadership of the ACR Neuroradiology Research Committee and the ACR Commission on Neuroradiology. With 50 years of research experience and more than 150 full-time research staff, the ACR's Center for Research and Innovation (CRI) project portfolio includes over 500 clinical research trials, and 2 million images processed annually. Section 6.3 outlines the ACR's role and responsibilities as the ALZ-NET operations center in greater detail.

Brown University Statistical Center

The Center for Statistical Sciences (CSS) of the Brown University School of Public Health will serve as the statistical center for ALZ-NET. The CSS has extensive expertise and experience in the evaluation of diagnostic and screening modalities. The ALZ-NET lead statistician is Dr. Constantine Gatsonis, Director of CSS and Chief Statistician of the NOPR, the IDEAS Study program and world-renowned expert in diagnostic imaging statistical methods and analysis. CSS faculty and staff provide methodological expertise, leadership, and support in all phases of ALZ-NET, including design, study monitoring, analysis of clinical and medical claims data and preparation of reports and manuscripts.

American Society of Neuroradiology (ASNR)

The ASNR was founded in 1962 in New York and is the largest professional society representing neuroradiologists and the specialty of neuroradiology. The ASNR is headquartered in Oak Brook, Illinois. ASNR has over 5,000 members who practice in hospital settings, academic institutions, government/military branches, and private practice. The ASNR is the preeminent organization in North America regarding neuroimaging and has many collaborative relationships. As part of its mission, it promotes the highest standards for clinical practice, education, and research in neuroradiology. The ASNR is committed to propagating evidence-based medical information.

Research Community and Other Partners

ALZ-NET also aims to collaborate with additional organizations that have broad scientific, research and clinical interest in AD treatment and diagnostics. These organizations include federal agencies (i.e., the Centers for Medicare & Medicaid Services (CMS), the Food and Drug Administration (FDA), the National Institute of Aging (NIA), etc.), the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and various pharmaceutical companies of affiliated studies. Representatives from these organizations provide additional expertise and perspective to the ALZ-NET Project Team.

6.3 ALZ-NET Operations Center

The ACR Center for Research and Innovation (CRI), based in Philadelphia, Pennsylvania, will serve as the operations center for ALZ-NET. As the operations center, the ACR has complete oversight and responsibility for conducting the research initiative under an agreement with the Alzheimer's Association to assist in initial development and ongoing management of ALZ-NET. Broadly, these responsibilities include:

- Oversight and management of study documentation and regulatory compliance.
- Recruiting and contracting with participating sites
- Creation and management of the ALZ-NET database; collection, transfer and archiving of data and images.
- Management of all funds; to include collection, accounting, and distribution of funds

The daily activities undertaken within the operations center are conducted according to International Conference on Harmonization Good Clinical Practice Guidelines, applicable government regulations (e.g., Title 45, Part 46 Code of Federal Regulations), standards of scientific integrity (i.e. ICMJE and Agency for Healthcare Research and Quality), and the American College of Radiology (ACR) research policies and procedures.

6.4 Single Institutional Review Board (IRB) of Record

ALZ-NET is contracted with an established central Institutional Review Board (IRB) to serve as the IRB of record for ALZ-NET. All participating sites are obligated to use the assigned central IRB as the IRB of record for ALZ-NET activity at their site. Local IRB stamp of approval or acknowledgement is allowed per local policies, but oversight of ALZ-NET conduct must be ceded to the central IRB. The ALZ-NET website provides detailed instructions and resources on use of the central IRB, including cessation of review, initial submissions and general ongoing operations. The use of a central IRB ensures that ALZ-NET remains in compliance with the Health and Human Services (HHS) revised Common Rule on use of a single IRB (45 CFR 46). The ALZ-NET operations center aims to lower site regulatory burden by streamlining regulatory operations, document review, and associated costs.

7.0 PARTICIPATING SITE REGISTRATION REQUIREMENTS

Participating sites will be recruited from the IDEAS Study network, affiliations with the Alzheimer's Association and partnering organizations, applicable national societies, as well as media outreach. All interested sites must complete a site feasibility and registration questionnaire in order to receive an invitation from ALZ-NET to participate. This site feasibility and registration questionnaire will be located on the ALZ-NET website. Each participating site must demonstrate the use of a multi-disciplinary dementia care team and optimal medical management. It is expected that participating sites have clinical expertise and an infrastructure to evaluate patients and provide novel FDA-approved AD therapies consistent with the safety monitoring outlined in applicable FDA approved labels. Aspects of a qualified participating site include, but are not limited to, access to accredited and appropriate radiological services for diagnostic and safety brain imaging; access to infusion services; access to emergency services; and access to standard cognitive, behavioral, and functional assessments used in dementia care.

If approved to become a participating site, a welcome packet will be emailed to site contacts, including all essential documents and instructions to complete the start-up process. Mandatory start-up activities that must be completed before a site receives full activation approval and prior to any patient consent include:

- IRB approval by ALZ-NET's IRB of record (see section 6.4).
- Fully executed contractual agreement between the site and the ACR (ALZ-NET's operation center).
- Provision of a Form W-9 to the ACR to facilitate payment for time and resource requirements of data submission.
- Having at least one approved site investigator (see section 8.0 for approval criteria).

7.1 Site Registration Elements

Data elements about participating sites will be collected during the site feasibility and registration process. These data are required to be entered via the ALZ-NET Site Feasibility and Registration Form which is located on the ALZ-NET website for electronic submission. Contact information and site address will be recorded for operational purposes. Data collected to describe the characteristics of multi-disciplinary dementia care team include but are not limited to:

- Utilization of physician extenders
- Licensing and access to cognitive, function, and behavioral assessments
- Access to infusion services
- Access to accredited imaging services

Data collected to describe patient population and enrollment feasibility include but are not limited to:

- Race and ethnicity percentages of patient population
- Estimated enrollment capabilities based on the ALZ-NET eligibility criteria

8.0 SITE INVESTIGATOR REQUIREMENTS

Each site investigator, otherwise known as a prescribing clinician, must complete a user profile request in order to be considered an approved user and receive access to the ALZ-NET Electronic Data Capture (EDC)system. The request for a user profile must be completed via the Staff Registration Questionnaire found on the ALZ-NET website. For the purpose of ALZ-NET, the main criterion to be considered a site investigator is to hold credentials that authorize the prescription of novel FDA-approved therapies for patients with AD. Clinical practices and clinical research groups are increasingly using advanced practice providers (APPs) to deliver care and conduct research, therefore ALZ-NET is allowing APPs with prescribing authority to serve as site co-investigators. Any APPs that serve as a site investigator must carry out their duties as an ALZ-NET investigator under the same conditions as they would manage other aspects of dementia patient care. In other words, APPs should not exercise greater than their usual independence when prescribing novel AD therapeutics and monitoring patients for potential adverse events. It is expected that all site investigators have appropriate education and a substantial proportion of contact time for the evaluation and care of adults with acquired cognitive impairment or dementia.

To be approved to participate in ALZ-NET, each site investigator must also:

- Review all applicable FDA prescribing labels and published Appropriate Use Recommendations for novel FDA-approved therapies for AD.
- Complete the ALZ-NET operations training modules on the ALZ-NET website.
- Complete training for research with human subjects (e.g., CITI, ACRP, Advarra IRB).
    - Documentation of human subjects training must be uploaded within the ALZ-NET Site Personnel Registration Form for all site investigators. Site staff who are designated as having consenting authorization by their site's principal investigator also need to upload documentation of training.
    - Documented training must have occurred within 3 years prior to profile registration.
    - If training is needed, ACR will cover the cost through affiliation with CITI. Users may affiliate with the American College of Radiology during their CITI registration process in order to complete the "Human Subject Research – Basic" course, free of charge.
    - Advarra IRB also offers a web-based training program that fulfills the human subject protection training requirement and generates a certificate of completion.
- Obtain access and complete training specific to the ALZ-NET Electronic Data Capture (EDC) system.

8.1 Site Investigator Registration Elements

Data elements about participating site investigators will be collected during the staff registration process. These data are required to be entered via the ALZ-NET Site Staff Registration form, which is located on the ALZ-NET website for electronic submission. The investigator's name and contact information are solely collected for operational and ALZ-NET conduct purposes (i.e., access to ALZ-NET applications, sponsor communications, verification of prescribing authorization, etc.). National Provider Identifier (NPI) number will be collected in order to verify prescribing authority as well as review non-identifiable data from the NPI profile (i.e., gender). Additional data elements that will be collected to review prescribing trends of novel FDA-approved AD therapies include:

- Type of provider
- Board certifications and sub-specialties
- Experience in dementia care
- Experience with novel FDA-approved AD therapies

9.0 SITE STAFF REQUIREMENTS

Each staff member who will be assisting with the data collection and conduct of the registry at a site must complete a user profile request in order to be considered an approved user and receive access to the registry's Electronic Data Capture (EDC) system. The request for a user profile must be completed via the Staff Registration Questionnaire found on the ALZ-NET website.

To be approved to participate in ALZ-NET, each site staff must also:

- Complete the ALZ-NET operations training modules on the ALZ-NET website.
- Complete training for research with human subjects (e.g., CITI, ACRP, Advarra IRB).
    - Documentation of human subjects training must be uploaded within the ALZ-NET Site Personnel Registration Form for all site staff who are designated as having consenting authorization by their site's principal investigator.
    - Documented training must have occurred within 3 years prior to profile registration.
    - If training is needed, ACR will cover the cost through affiliation with CITI. Users may affiliate with the American College of Radiology during their CITI registration process in order to complete the "Human Subject Research – Basic" course, free of charge.
    - Advarra IRB also offers a web-based training program that fulfills the human subject protection training requirement and generates a certificate of completion.
- Obtain access and complete training specific to the ALZ-NET Electronic Data Capture (EDC) system.

10.0 PATIENT CONSENT, ELIGIBILITY, AND REGISTRATION

10.1 Informed Consent

The site investigator and/or authorized designee will obtain informed consent using the IRB-approved informed consent form (ICF). If the patient is determined by the site investigator to lack capacity, a legally authorized representative (LAR) or proxy consent will be allowed. A face to face, in-person informed consent process is the preferred best practice; however, remote and electronic consent is allowed using a 21-CFR part 11 compliant signature platform. LAR and remote or electronic consent are allowed provided the research personnel comply with all IRB, institutional, state, and federal guidelines. Electronic consent forms must be separately approved by the IRB of record before use. The remote and electronic informed consent processes should occur in a way that is similar to what would be conducted in-person under normal circumstances. These conversations may occur via telephone, conference call, video conferencing, telemedicine, or other methods used by the consenting site. The IRB approved informed consent must be sent to the patient prior to engaging in the informed consent conversation, so the patient can reference the document during the conversation.

When obtaining remote consent, researchers must document (1) how the ICF was transmitted to the patient (e.g., email, fax, mail, etc.) and (2) how the patient's signature was obtained. The consenting site must ensure the fully executed ICF is returned to the study team. All patients, or their proxies as appropriate, will provide consent to allow access to their healthcare data to complete study electronic case report forms (eCRFs) as well as their health insurance claims data for follow-up purposes. If a site is planning on obtaining informed consent remotely, thorough guidance can be found on the study website. Participation in any of the optional components in ALZ-NET will require explicit consent to each of the components within the main informed consent document.

10.2 Eligibility Criteria

All eligibility criteria must be confirmed by the site investigator (prescribing clinician) using the patient's medical records, prior to registration. The ALZ-NET protocol will be conducted in individuals over the age of 18 who are being evaluated for or treated with a novel FDA-approved AD therapy in a real-world clinical setting. The decision to prescribe treatment will be based on clinical assessment by the site investigator and independent of the decision to enroll the individual in ALZ-NET, with adherence to the label and any relevant appropriate use recommendations.

NOTE: Other protocol-defined Inclusion/Exclusion criteria may apply for affiliated studies.

10.2.1 Inclusion Criteria

To be eligible to participate in ALZ-NET, candidates must meet the following eligibility criteria at screening/enrollment or at the time point specified in the individual eligibility criteria listed:

1. Patient or patient's legally authorized representative (LAR) (e.g., spouse or legal guardian) has the ability to understand the purpose and risks of ALZ-NET and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local patient privacy regulations.
2. Patient is at least 18 years of age at the time of informed consent.
3. Patient has a diagnosis of MCI or dementia with clinical suspicion of Alzheimer's disease (AD) as contributing pathology and 1) is being evaluated for treatment or 2) will be initiating treatment or 3) has already initiated treatment with novel FDA-approved AD therapies in real world clinical practice
4. If treatment is initiated at time of consent, the patient meets appropriate label requirements and treatment follows appropriate use recommendations for novel FDA-approved AD therapy/therapies.
5. Patient's treating clinician has made the decision to provide clinical care or treatment prior to patient consent and independently of the purpose of ALZ-NET.

10.3 Patient Registration

Patients or their legally authorized representatives, where applicable, must provide informed consent before any data is collected for purposes of registration into ALZ-NET. Patient eligibility for ALZ-NET must be determined prior to registering the patient into ALZ-NET. Full eligibility criteria for participation in ALZ-NET can be found in section 10.2. Confirmation of eligibility will be recorded during the patient's registration process by the consenting site. The decision to evaluate and treat the patient with a novel FDA-approved AD therapy is at the discretion of the treating clinician and should be determined independently of and prior to ALZ-NET participation.

Patient registration is available to activated clinical sites 24 hours a day, seven days a week via the ACR's research management system. Upon patient registration to ALZ-NET, an electronic copy of the registration/eligibility data will be available in Medidata Rave, the ALZ-NET electronic data capture (EDC) system. The ACR's research management system integrates with Rave to generate the case record and begin the data collection and monitoring process. Enrollment into ALZ-NET is defined as the date the patient is registered in the ACR's research management system.

After the registration of the patient, all further data collection will be captured by one of the available data transfer mechanisms provided by the ALZ-NET and then ingested and stored in Medidata Rave. Section 11.1 provides additional detail on available data transfer mechanisms. Enrollment is defined for ALZ-NET as the date in which the patient is registered in the ACR's research management system. Upon registration, patients will be assigned a unique patient identification number by which all clinical and imaging data will be identified. Any patient identification numbers that are assigned will not be reused even if the patient appropriately re-enrolls in ALZ-NET. For information related to patient re-enrollment, refer to section 11.9.

10.4 Co-enrollment In Affiliated Studies

ALZ-NET will work with affiliated studies to ensure seamless co-enrollment of patients being evaluated for or receiving a novel FDA-approved treatment for AD. This collaboration structure is designed to reduce the operational burden of participating sites and patients. Patients may be required to provide separate informed consent authorization for any affiliated studies to which they co-enroll. A separate registration process and confirmation of eligibility may also occur for the affiliated study; however, any overlapping data elements being collected by ALZ-NET and an affiliated study will only require data entry one time. All sites and patients should refer to applicable affiliated study protocols and informed consent forms for additional information, as some affiliated studies may not require any additional consent or tasks for participation.

11.0 ALZ-NET DESIGN & DATA PROCEDURES

ALZ-NET is a national, volunteer provider-enrolled longitudinal cohort registry designed to address key scientific and clinical questions on long term safety, clinical use and outcomes for patients being evaluated for or treated with novel FDA-approved therapies for AD. Treatments will be prescribed at the prescribing clinician's discretion. Patients will be monitored by the treating clinician according to patient needs and local standard of care (SOC).

ALZ-NET will collect data that characterizes patient demographics, diagnosis, medical conditions, comorbidities, co-pathologies, concomitant medications, and cognitive and functional status at enrollment and longitudinally at follow-up intervals. ALZ-NET will also capture data related to biomarker results from imaging and biofluids (if applicable), safety outcomes, and healthcare resource utilization. This protocol for retrospective and prospective human subjects research will be conducted according to the International Conference on Harmonization Good Clinical Practice Guidelines, applicable government regulations (e.g., Title 45, Part 46 Code of Federal Regulations), and the ACR research policies and procedures.

To achieve sufficient data for ALZ-NET, patients will be monitored if they are evaluated for treatment, throughout treatment duration, and following treatment completion for as long as they are willing. Patients may stop using any novel FDA-approved therapy for AD, or any other commercially available non-investigational AD therapy, during their ALZ-NET participation period. Patients who discontinue the FDA-approved therapy for AD will continue to be followed for the duration of ALZ-NET with all clinical evaluations, until one of the participation endpoints is met (see section 11.8). The table below provides a summary of data that will be reported within the EDC as part of ALZ-NET. For a specific schedule of forms and data elements that are reported within the EDC at specified data collection timepoints, refer to the *ALZ-NET Summary Table of Data Elements* and *Case Report Form (CRF) packets* on the ALZ-NET website.

ALZ-NET DATA COLLECTION	SITE START-UP[1]	PATIENT REGISTRATION (ENROLLMENT)[2]	PATIENT PARTICIPATION[3]
Participating Site Characteristics	x		
Site Investigator (*Prescribing Clinician*) Characteristics	x		
Informed Consent		x	
Eligibility Checklist		x	
Patient Demography		x	
Patient Information		x	
Concurrent Study Enrollment			x
Patient Characteristics			x
Medical History			x
Lifestyle Data			x
Vital Signs			x
Clinical Features			x
Additional Measures (*Cognitive, Functional, and Behavioral*)			x
Clinical Events			x
Concomitant Medications			x
AD Diagnosis			x
Diagnostic Testing			x
Clinical Imaging Submission[4]			x
Imaging Assessment[5]			x
AD Treatment and Dosing Log			x
Healthcare Utilization (*Hospitalizations and ER Visits*)			x
Adverse Events (AEs) / ARIA Adverse Events			x
End of Participation (Death, Lost to Follow-up, Withdrawal of Consent) – *only if applicable*			x

1) Information submitted via the site registration questionnaire and staff registration questionnaire on the ALZ-NET website.
2) Data submitted during the patient registration process via the ACR's research management system. The date of patient registration becomes the date of the baseline timepoint for data entry.
3) Data submitted via one of the ACR approved clinical data transfer mechanisms at applicable data collection time points (i.e. baseline and/or follow up).
4) Transmission of brain images occurs via ACR's CONNECT and TRIAD applications.
5) Image assessment data are captured from submitted radiology reports.

11.1 Clinical Data Submission

ACR uses Medidata Rave, a 21 CFR Part 11 compliant online electronic data capture system (EDC) and data management system, consistent with the Food and Drug Administration's (FDA's) Guidance for Industry: Computerized Systems Used in Clinical Trials. Access to studies, sites, and patients is based on a user's assigned roles. To submit data, the appropriate investigator-designated research staff will receive an invitation to Medidata Rave, which will allow the user to activate their account. Once the user activates their account, they will have access to the site-specific study forms and associated eLearnings.

After completing any necessary training modules, the user will be able to enter data directly into the electronic case report form (eCRF) using an up-to-date internet web browser. Upon saving the data, preprogrammed edit checks look for discrepant or inconsistent data and automatically sends system generated queries to the site users, providing them with immediate feedback. In addition to system-generated queries, data managers can send manual queries to sites regarding patient data. Authenticated site staff will have view restrictions to only the data they submitted to ALZ-NET.

In addition to the option of site staff entering data directly into the EDC for registry patients, other data transfer mechanisms will be available for sites to utilize for applicable patient clinical data. These mechanisms will be available to minimize manual data entry by the site into the EDC. Data ingestion will be facilitated by a collection of applications if the participating site chooses. These applications include ACR CONNECT, HL7 Listener, sFTP, Webform with Validation, and API. Only authenticated users will be permitted to access the applications and ALZ-NET platform.

Each of these applications support the push or pull-in of information to ALZ-NET - parsing, validating, and de-identifying data. For more detailed information on specific procedures and requirements for automated data extraction and transfer, contact the ACR operations team.

11.2 Overall ALZ-NET Baseline and Follow-Up Time Points

Patients will be enrolled into ALZ-NET by a prescribing clinician at an activated site at the time the decision has been made to evaluate the patient for or treat the patient with a novel FDA-approved therapy for AD independent of the purpose of ALZ-NET, or when the site has full documentation that treatment has already been initiated. This timepoint for data collection represents a baseline for longitudinal evaluation. Treatments will be prescribed at the prescribing clinician's discretion. Patients will be monitored by the treating clinician according to patient needs and local standard of care (SOC), in alignment with appropriate use recommendations (AUR). All references to forms that must be submitted refer to completed within the EDC. If a site's SOC does not capture data to fill out a form during a particular timepoint, the form must still be submitted as directed within the EDC.

Patients will participate in ALZ-NET in perpetuity, until one of the participation endpoints is met. Participation in ALZ-NET requires the patient to visit their dementia care site according to the site's normal schedule for follow-up visits, despite their involvement in ALZ-NET. As long as consent is active and the patient continues to receive care, data will be collected and provided to ALZ-NET in accordance with the applicable follow-up data entry time points described in section 11.4 below. A detailed table of data elements and definitions of required and optional clinical evaluations is available as a supplemental resource on the ALZ-NET website or by contacting the ALZ-NET operations center. Site staff should reference all training materials and resources on the ALZ-NET website for additional detail on the data being collected.

11.3 Baseline Data Collection Time Point

Patients who meet eligibility criteria and are registered as a patient in ALZ-NET will receive their standard dementia care as they would without their participation in ALZ-NET, aligned with applicable appropriate use recommendations and FDA labeling for novel FDA-approved therapies for AD.

The baseline data collection timepoint captures the clinical assessment and associated data outlined in the table above in section 11.0, for the time period up to and including the day of enrollment into ALZ-NET, regardless of whether treatment with a novel therapy has been initiated. The baseline time point serves to collect applicable patient characteristics, medical history, concomitant medications, previous diagnostic procedures, and baseline scores for standard cognitive, functional, and behavioral assessments. The baseline data elements should be recorded in the patient's medical record and then extracted and transmitted to ALZ-NET via one of the approved data transfer mechanisms.

11.4 Follow-Up Data Collection Time Points

Given the voluntary and post marketing nature of the ALZ-NET platform, all activities related to a patient's ongoing care management will be conducted at the prescribing clinician's discretion and standard of care (SOC). There are no prescribed or required 'site visits' related to data collection. The prescribing clinician should refer to the current and applicable FDA-approved AD therapy product label for recommended evaluation, dosing, and safety monitoring plan. Any clinical visits occurring after patient enrollment should capture data associated with the prescribing clinicians SOC and reported at the follow up data collection time points. The data elements outlined in the table above in section 11.0 should be recorded in the patient's medical record and then entered or extracted and transmitted to ALZ-NET via one of the approved data transfer mechanisms. ALZ-NET requires participating sites to complete follow-up clinical data forms within the EDC at the following time windows after baseline:

- 6 months
- 12 months
- 18 months
- 24 months
- Annually thereafter until a participation endpoint is met.

If no visit occurs within the windows above, the site must indicate so on the appropriate form within the EDC. If multiple clinical visits occur between two data collection time points, the data entered into the EDC should be from the most recent point in time that data element was assessed. However, some data elements such as adverse event reporting, healthcare encounters, and changes in concomitant medications should be reported using the data within the medical record from the entire time period. Sites should follow the instructions found on the specific case report from, as well as in section 12.0 below, to determine which data is required for submission. While ALZ-NET is collecting these data, ALZ-NET is not collecting these data in real-time. To confirm, real-time reporting of AEs/SAEs, including ARIA AEs/SAEs, should be reported through the standard methods to either the sponsoring company or MedWatch, as appropriate.

Data forms and assessments that are required to be completed at each data collection time point are outlined in the table above in section 11.0 as well as the supplemental resources found on the ALZ-NET website. During follow-up time windows, every effort should be made by the participating site to complete the required data forms. Assessments via telemedicine are permitted if a patient or an informant/care partner is unable to visit the clinic in person. It is intended that all eligible patients be followed for the entire duration of their participation in ALZ-NET or until death, withdrawal, or lost to follow-up. Eligible patients will be followed, even if they discontinue treatment with an FDA-approved AD therapy, unless informed consent is withdrawn.

11.5 Discontinuation or Change of Treatment

Patients who are enrolled in ALZ-NET but switch treatments, or discontinue treatment altogether, will continue participating in ALZ-NET until death, withdrawal of informed consent, or lost to follow-up. The treating clinician will record the primary reason for drug change or discontinuation, including any AEs leading to the decision. Information will be collected at routine clinical visits as per the protocol for the extent of the patient's participation in the study. If treatment changes or discontinuation occur due to a safety event that may be specific to a novel FDA-approved AD treatment, information will be collected through resolution of that event. For example, in the case of monoclonal antibody anti-amyloid treatments, the incidence and management of amyloid related imaging abnormalities (ARIA) will be captured.

11.6 Transfer of Care

Patients who decide to transfer their care from one prescribing clinician to another while participating in ALZ-NET are able to continue their participation as long as the new treating clinician is an approved ALZ-NET investigator. The new treating clinician may be at the same participating site or at another site that is also participating in ALZ-NET. If the patient transfers to a new participating site, re-signing of the informed consent may be required prior to the case being transferred within the EDC.

11.7 Protocol Deviations/Protocol Violations

A protocol deviation/protocol violation occurs when the patient, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion criteria, exclusion criteria, subject safety, and primary endpoints of a protocol. Any protocol deviations/protocol violations must be reported to the IRB within 2 weeks (10 business days) from the time the violation was identified. Discovery of a protocol deviation/protocol violation should result in an immediate email communication to ALZNET-Regulatory@acr.org.

Protocol violation documentation will require the following:

1. Case # and Advarra Protocol #
2. Description of the violation
3. IRB acknowledgement, note that IRB will review at the next quarterly review period, or IRB feels this deviation does not warrant review.
4. Corrective action plan (CAPA) to prevent future occurrence of the same protocol deviation/protocol violation.
5. Ensure that all information provided by Site is Redacted.

Protocol violations may include, but are not limited to:

1. Patient consented with ICF which had been changed without IRB approval.
2. Patient consented with non-current ICF.
3. Patient enrolled without consent.
4. Patient enrolled to a protocol version which had been changed without IRB approval.
5. Patient enrolled under expired IRB approval.
6. Inclusion/exclusion criteria not met at time of enrollment to registry.
7. There was a breach in patient confidentiality.

11.8 End of Participation

ALZ-NET has no defined End Visit for patient participation. As long as an enrolled patient continues to receive care from a participating ALZ-NET provider, and does not withdraw their consent to participate, ALZ-NET will collect data specified in section 11.0. A patient's participation in the ALZ-NET can be terminated by one of the following ways: withdrawal of consent (see section 11.8.1 below), meeting the ALZ-NET definition of Lost to Follow-Up (see section 11.8.2, below), death, closure of ALZ-NET, or termination of the current provider site's participation in ALZ-NET.

11.8.1 Withdrawal of Consent

Patients may withdraw consent to participate in ALZ-NET at any time with no effect on their medical care or access to treatment. If withdrawal occurs during a routine clinical visit, the prescribing clinician will collect information one last time following the standard protocol if permitted by the patient. If a patient withdraws from the study outside of the clinician's office, information will be collected one last time by telephone according to the standard protocol if permitted by the patient.
Patients may be withdrawn from ALZ-NET for any one of the following reasons:

- The patient or LAR, if applicable, withdraws consent.

- The patient or LAR, if applicable, is unwilling or unable to comply with the protocol.

The reason for the patient's withdrawal from ALZ-NET must be recorded in the registry's EDC. All information already collected as part of ALZ-NET will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

11.8.2 Lost to Follow Up

Patients will be considered lost to follow-up if they miss 3 consecutive data collection timepoints (for assessment by the prescribing clinician or site staff) and are unable to be contacted by the participating ALZ-NET site. At least 3 contact attempts should be documented in the patient's medical record including the method of contact such as phone, letter, email, text, or certified mail. Should the patient continue to be unreachable, that patient will be considered to have discontinued participation from ALZ-NET with a primary reason of lost to follow-up. Lost to follow-up patients are able to resume participation if contact is made and their consent to participate is not withdrawn.

11.8.3 Death

If an ALZ-NET site is notified of the death of an ALZ-NET patient, the death must be documented in the patient's medical record. The Death Details form must be completed to include the date of death and the primary cause of death.

11.9 Screening and Re-enrollment

Patient screening is the process of evaluating a patient for the protocol's inclusion eligibility. It is not the process of evaluating the patient for treatment. ALZ-NET does not capture data on screen failures. ALZ-NET does capture data on patients who may not end up receiving treatment after enrollment. After a patient fails screening, becomes ineligible, withdraws from ALZ-NET, is lost to follow-up, or transfers care to a new provider or site, patients may re-screen and re-enroll in ALZ-NET as long as all eligibility criteria are re-assessed and met at time of re-enrollment. Re-enrollment will require initiating the ALZ-NET process as a new patient. Sites are able to provide the original patient identification number at the time of re-registration so that prior data can be aggregated appropriately.

12.0 ALZ-NET DATA ELEMENTS

A detailed table of data elements and time points is available as a supplemental resource that is available on the ALZ-NET website or by contacting the ALZ-NET operations center. The below sections outline the core data elements to be reported for each registered patient in ALZ-NET. Treatments will be prescribed at the prescribing clinician's discretion. Patients will be monitored by the treating clinician according to patient needs and local standard of care (SOC), in alignment with appropriate use recommendations (AUR). All references to forms that must be submitted refer to completed within the EDC. If a site's SOC does not capture data to fill out a form during a particular timepoint, the form must still be submitted as directed within the EDC.

12.1 Patient Registration (Enrollment)

The data captured during the patient case registration process will be collected only at the time of enrollment for all patients. Patient enrollment is completed by authorized site staff within the ACR's research management system. Informed consent data will be collected to capture the appropriate regulatory process.

Eligibility confirmation, patient demographics and identifiable information will be reported to ALZ-NET during the enrollment process. ALZ-NET collects certain identifiable information to collect claims data from the patient's healthcare insurer. Each patient must provide consent and authorization to the collection of their identifiable data via the informed consent process, prior to registration in ALZ-NET. All protected health information (PHI) will remain encrypted and securely stored separate from the clinical and imaging data captured by ALZ-NET.

12.2 Concurrent Study Enrollment

Concurrent study enrollment data is submitted at the baseline and follow-up time points for all registered patients via one of ALZ-NET's available data transfer mechanisms. This data will inform ALZ-NET if the patient has been enrolled in any non-affiliated and affiliated studies, which may dictate the package of eCRFs that become available at applicable data entry time points.

12.3 Patient Characteristics

Patient characteristic data is submitted at the baseline time point for all registered patients via one of ALZ-NET's available data transfer mechanisms. This data captures applicable sociodemographic and social determinants of health characteristics for ALZ-NET patients.

12.4 Medical History

Medical History data is submitted at the baseline time point for all registered patients via one of ALZ-NET's available data transfer mechanisms. Baseline data includes the most recent assessment prior to, and including, the day of registration. Medical history data captures start dates, current status, and end date, if applicable, on specific pre-populated patient diagnoses and co-morbidities. All pre-populated diagnoses must be assessed at the baseline time point. There is also the ability to add additional log lines in order to report on any other, relevant medical history conditions.

12.5 Lifestyle Data

Lifestyle data is submitted at the baseline time point for all registered patients via one of ALZ-NET's available data transfer mechanisms. This data captures common habits that may constitute comorbidities (e.g., tobacco and alcohol use). Lifestyle data can also be reported at follow-up time points, if applicable to the patient.

12.6 Vital Signs

Vital Sign data is submitted at the baseline and follow-up time points for all registered patients via one of the registry's available data transfer mechanisms. Baseline data includes the most recent assessment prior to, and including, the day of registration. If vital sign data were collected multiple times during an applicable data collection time period, site staff should enter the data associated with the most recent date of vital sign assessment.

12.7 Clinical Features of Co-pathology

Clinical features of co-pathology data are submitted at the baseline and follow-up time points for all registered patients via one of ALZ-NET's available data transfer mechanisms. These co-pathologies describe a list of symptoms and signs that clinicians may identify evidence of during the clinical history and standard neurological exam, even if patient has not yet received a formal diagnosis. These co-pathologies are important to evaluate, as any positive findings would exclude patients from most clinical trials and may be missed if only assessed by formal diagnoses.

12.8 Additional Measures (Cognitive, Functional, and Behavioral)

Additional measures data is submitted at the baseline and follow-up time points for all registered patients via one of ALZ-NET's available data transfer mechanisms. This data captures details of clinical assessments conducted within standard dementia care, including cognitive, functional, and behavioral assessments. Data collected about the performed assessments include total scores and date performed. All assessments should be conducted in the patient's preferred language by trained staff that have appropriate knowledge on the use of the assessment.

Required assessments in each of the data collection time points include:

- Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA)
- Functional Activities Questionnaire (FAQ)

Optional assessments in each of the data collection time points include:

- AD8 Dementia Screening Interview
- Neuropsychiatric Inventory Questionnaire (NPI-Q)

12.9 Concomitant Medications

Concomitant Medication data is submitted at the baseline timepoint and reassessed for changes at all follow-up time points for all registered patients via one of ALZ-NET's available data transfer mechanisms. This is collected in an open log format that captures all the medications that a patient is currently prescribed. At baseline, the patient's current medications log from the EHR should be captured on the eCRF. Data elements include start and stop dates, indication, and dosing details. At the follow-up time points, any newly prescribed medication or changes to medication should be captured. All changes that occur to a patient's medication during a data collection time period should be recorded in the medical record and provided to ALZ-NET.

Novel FDA-approved AD therapies (approved after 2021) whether they are designed to be disease modifying (slow disease progression) or treat symptoms (cognitive, behavioral, or neuropsychiatric features) that a patient may be prescribed are captured on specific novel therapy (see section 12.15, AD Treatment and Dosing) forms within the EDC. Medications approved by the FDA before 2021 that treat cognitive symptoms of AD (e.g., donepezil, rivastigmine, galantamine, memantine) should be reported as concomitant medications.

12.10 AD Diagnosis

Alzheimer's disease diagnosis data is submitted at the baseline and follow-up time points for all registered patients via one of ALZ-NET's available data transfer mechanisms. This data captures clinical characteristics and diagnostic history of the patient's cognitive impairment.

12.11 Diagnostic Testing

Diagnostic testing data is submitted at the baseline and follow-up time points for all registered patients via one of ALZ-NET's available data transfer mechanisms. This data captures data about any diagnostic tests a patient has received. Data captured includes diagnostic imaging, fluid biomarkers (cerebrospinal fluid or blood-based), and APOE status that are completed either prior to or during the patient's participation in ALZ-NET.

12.12 Clinical Events

Clinical events data captures any patient diagnoses and co-morbidities which began during follow-up time periods that may or may not also meet Adverse Event reporting requirements. Similar to medical history, clinical events capture data on specific, targeted diagnoses and co-morbidities as well as the option to report other, specify. Data elements captured on this form include start dates, current status, and end date, if applicable.

12.13 Clinical Imaging

Clinical imaging data is submitted at the baseline and follow-up time points for all registered patients via one of ALZ-NET's available data transfer mechanisms. This data captures all MRI and PET imaging that a patient receives as part of their care. It also serves as a data verifying mechanism for ALZ-NET to reconcile what imaging has been reported within a particular data entry timepoint and what imaging data ALZ-NET has received as part of the image repository. All imaging that occurs during a data collection time period should be recorded in the medical record and reported to ALZ-NET. If novel therapy was

initiated prior to patient registration, submit data for the most recent imaging performed prior to the initiation of treatment and all imaging thereafter. If novel therapy was not initiated prior to registration, submit data for the most recent image performed prior to registration and all imaging thereafter. The type of imaging ALZ-NET collects data about include:

- Amyloid positron emission tomography (amyloid PET)
- Tau positron emission tomography (tau PET)
- Fluorodeoxyglucose-positron emission tomography (FDG-PET)
- Magnetic resonance imaging (MRI)

12.14 Imaging Assessment

Imaging Assessment data is extracted from the radiology reports submitted by the site via one of ALZ-NET's available data transfer mechanisms. The data extraction process is completed by ALZ-NET operational staff. Participating sites are responsible for submitting a radiology report for every image that is reported to ALZ-NET during the baseline and follow up time points. Data captured from submitted radiology reports includes diagnostic and safety data related to amyloid related imaging abnormalities (ARIA) in patients treated with FDA-approved anti-amyloid monoclonal antibodies. Participating sites should instruct their partnering imaging centers to review section 14.0, as well as the ALZ-NET website, for guidance on acquisition, reporting, and data transfer.

12.15 AD Treatment and Dosing

Novel therapy data is submitted at the baseline and follow-up time points for all registered patients via one of ALZ-NET's available data transfer mechanisms. All data related to AD treatment and dosing should be recorded in the medical record during a data collection time period and provided to ALZ-NET. This data captures any novel FDA-approved AD therapies (approved after 2021), whether they are designed to be disease modifying (slow disease progression) or treat symptoms (cognitive, behavioral, or neuropsychiatric features), that the patient was prescribed.. Note: Medications approved by the FDA before 2021 that treat cognitive symptoms of AD (e.g., donepezil, rivastigmine, galantamine, memantine) should be reported as concomitant medications (see section 12.9).

Dosing log data includes:

- Dose type (missed, titration, maintenance)
- Start and stop dates
- Dose level
- Change in treatment since the last dose and reason for the change in dosage

12.16 Healthcare Utilization (Hospitalizations and ER Visits)

Healthcare utilization data is submitted at all follow-up time points for all registered patients via one of ALZ-NET's available data transfer mechanisms. If a patient has already initiated treatment at the time of registration, this data also reported at the baseline timepoint. This data captures data about the number of, if any, hospitalizations or emergency room visits that may have occurred during a data collection time period.

12.17 Adverse Events (AEs) / ARIA Adverse Events

Adverse events (AE) and serious adverse events (SAE) data is submitted for registered patients that had a reportable event, as defined by section 16.0. All AEs and SAEs that meet the ALZ-NET reporting guidelines must have data provided to ALZ-NET via one of ALZ-NET's available data transfer mechanisms. Data elements captured include:

- Start and stop dates
- Outcome
- Severity

- Action taken with novel AD therapy
- Relationship to novel AD therapy
- Reporting details

All AEs and SAEs specific to ARIA will be captured on a separate ARIA Adverse Events form. This form allows ALZ-NET to correlate incidence of an ARIA event to the appropriate MRI Assessment form.

Additionally, it is expected that site staff and prescribing clinicians will follow standard FDA reporting procedures as outlined on applicable FDA labels of prescribed novel AD therapeutics. Reporting procedures may include directly contacting the applicable pharmaceutical company and/or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. Submission of adverse event data to ALZ-NET does not satisfy any other regulatory requirements for reporting. Participating sites should report all serious adverse events judged by the investigator to be possibly, probably, or definitely related to the compound of interest to the applicable pharmaceutical company (Marketing Authorization holder) within 24 hours of becoming aware of the event. ALZ-NET will not be reporting adverse events in real-time (within 24 hours of the event), so it is required that participating sites follow the standard procedures for reporting.

13.0 HEALTH INSURANCE CLAIMS DATA

To accomplish one of the ALZ-NET aims, "evaluate longitudinal health outcomes and track resource utilization", ALZ-NET will collect health insurance claims from enrolled patients. The ACR CRI Data Management Center and Brown University Statistical Center will coordinate the claims data collection and analysis. Proper informed consent and authorization to collect healthcare claims will be collected for all ALZ-NET patients via the IRB-approved ICF. A patient's informed consent will authorize collection of their health insurance claims data for a time period of five (5) years prior to their enrollment into ALZ-NET and in perpetuity ahead, unless consent is otherwise withdrawn. ALZ-NET will contract directly with applicable insurance companies to collect claims data specific to the data analysis purpose of ALZ-NET. No claims data will be stored in the primary data set of ALZ-NET that will be used for external data sharing and future research. Participating sites do not have any responsibility in tracking or reporting of claims data.

14.0 IMAGING CONSIDERATIONS

14.1 Image Acquisition Standards

All imaging procedures that ALZ-NET patients undergo should be conducted per local practice, applicable procedure standards and appropriate use guidelines. Participating sites should inform their partnering imaging facilities of the resources and acquisition recommendations that are provided on the ALZ-NET website. ALZ-NET provides recommended acquisition protocols for Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI). The available resources outline appropriate training, recommended scanner type, required sequences, and reporting guidelines and templates.

14.2 Image Transfer and Archival

ALZ-NET aims to develop a vast image repository of diagnostic and safety monitoring scans for use in future research. Brain images will be collected for all ALZ-NET patients. All brain imaging PET and MRI studies that are associated with baseline and follow-up time points during the patient's participation will be transferred to and stored at the ACR Imaging Core Laboratory for quality control review and future research. Images to be transferred and archived are only those that are conducted as part of the patient's regular care and medical record. Participating sites that do not have the ability to transmit patient DICOM images to ALZ-NET will have the option to identify the patient's imaging facility from a network of imaging facilities as part of the site's data entry process. ACR will first require a contract agreement with imaging facilities who qualify for participation under the ALZ-NET protocol to establish an ALZ-NET Imaging Network. Contracted imaging facilities performing standard of care imaging will provide brain images to ALZ-NET in accordance with OHRP regulations for institutions not engaged in

human research. ALZ-NET participants will provide authorization to share identifiable information (i.e. imaging accession number, date of service, and radiology report) as part of the informed consent process to facilitate the transfer of relevant imaging under oversight by the partnering site.

TRIAD (Transfer of Images and Data) is a data collection and exchange toolset that is utilized by over 20,000 radiology facilities to support clinical trials, registries, national accreditation, and a wide variety of other educational and quality programs. TRIAD can be installed on one or several computers of choice within the institutional "firewall" and on the institutional network. Internet access is required. The TRIAD application can then be configured as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory. When properly configured, the TRIAD software de-identifies, encrypts, and performs a lossless compression of the images before they are transferred to the ACR Imaging Core Laboratory image archive in Philadelphia. TRIAD allows for direct connectivity to local DICOM systems for automatic retrieval, validation, and de-identification as well as the ability to upload various forms of clinical data and other non-DICOM data types to support domains other than radiology. The TRIAD workflow supports end-to-end project activities and tracking as well as final integration with curation systems.

ACR CONNECT, the newest addition, adds greater local processing and federated learning to the research network. A container-based application that runs locally at a facility or in a private cloud, ACR CONNECT hosts a variety of applications that connect to local resources such as the PACS or EHR and facilitates the use of AI/ML on local data before or in lieu of those data leaving the institution. ACR CONNECT provides the ability to move complex data processing close to the point of acquisition and enable complex multi-pass workflow. An "app model" allows the flexibility to add components over time and provides fine-grained control over the workflow including project-specific business rules, such as integration with external systems, patient-ID mapping for privacy-preserving record linkage, data harmonization, and advanced analytics. Also supported are tasks such as federated learning so that local data sets can be contributed without that data leaving the site. The ALZ-NET website provides additional instruction and contact information for image submission procedures.

15.0 BIOREPOSITORY OVERVIEW

An important aim of ALZ-NET is to establish a biorepository to collect and archive biosamples for future research. The biorepository infrastructure will be outlined within an associated laboratory manual once the contracting and operations are finalized. The initial launch of ALZ-NET does not include any biosample collection or archival. Once launched, participation in the biorepository will be optional for ALZ-NET sites and patients.

16.0 SAFETY DEFINITIONS AND REPORTING

16.1 Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a patient and does not necessarily have a causal relationship with their direct clinical care or treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physiological finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the standard of care medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

A pre-existing condition is one that is present at the start of the patient's participation in ALZ-NET. The pre-existing conditions which are of special interest to the protocol team are captured on the patient's Medical History form. In addition, after enrollment, conditions which don't meet the requirements of an AE but are of special interest are captured on the Clinical Events form. Medical History and Clinical Event conditions will be captured as an AE if the frequency, intensity, or character of the medical condition worsens during the patient's participation in ALZ-NET and meets the ALZ-NET reporting guidelines.

AEs, as defined above, experienced by patients participating in ALZ-NET are reported on the appropriate case report form, if at least one of the following criteria is met:

- Expected AEs per FDA label of the prescribed novel AD therapeutic
- Unexpected AEs that are considered to be possibly, probably, or definitely related to a novel FDA-approved AD therapeutic.
- AEs that cause a change in management of the prescribed novel FDA-approved AD therapeutic
- Events associated with the prescribed novel FDA-approved AD therapeutic(s), in the opinion of the site investigator (attribution categories of possible, probable, and definite).
- All serious adverse events (SAEs)

All AEs should be recorded using acceptable diagnoses and medical terminology. If an AE has already been reported, it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if myocardial infarction is reported as an AE, there is no need to report elevated creatine phosphokinase, or other related signs, symptoms, or laboratory values as separate AEs.

Attribution is used to determine whether an AE is related to a study treatment or procedure. Attribution categories are:

Definite:	The AE is **clearly related** to a treatment or procedure
Probable:	The AE is **likely related** to a treatment or procedure
Possible:	The AE **may be related** to a treatment or procedure
Unrelated:	The AE is **clearly not related** to a treatment or procedure

AEs may be **expected** or **unexpected**:

- An **expected AE** is one that is described in the protocol, the ICF, or the FDA label of the prescribed AD therapy.
- An **unexpected AE** has not been described in the protocol, the ICF, or the FDA label of the prescribed AD therapy.

Clinical severity of the reportable adverse events, including serious and non-serious events, should be assessed based on the following guidance:

- **Mild** - Discomfort noticed, but no disruption of normal daily activity.
- **Moderate** - Discomfort sufficient to reduce or affect normal daily activity.
- **Severe** - Incapacitating, with inability to work or to perform normal daily activity.

Reporting of AEs is the responsibility of each investigator and delegated staff engaged in ALZ-NET at a participating site. Anyone uncertain about whether a particular AE should be reported should contact the ACR for assistance. Each reported AE should be followed for the duration of the patient's participation in ALZ-NET or until resolution or stabilization. Source documentation must be available in the patient's medical record.

NOTE: If the event is a Serious Adverse Event (SAE) (see next section), further reporting will be required.

16.2 Serious Adverse Events

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- Results in death;
- Is life-threatening (at the time of the event);
- Requires inpatient hospitalization or prolongation of an existing hospitalization;
- Results in persistent or significant disability or incapacity;

- Is a congenital anomaly/birth defect;
- Is considered a medically important event.

Medically important events are those based upon appropriate medical judgment that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the patient and may require intervention to prevent one of the other serious outcomes noted above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.) An ARIA event is not automatically considered an SAE unless it meets one of the defined criteria above.

SAEs, as defined above, experienced by patients participating in ALZ-NET should be reported in the SAE section of the appropriate case report form. Source documentation must be available in the patient's medical record.

Additionally, it is expected that site staff and prescribing clinicians will follow standard FDA reporting procedures as outlined on applicable FDA labels of prescribed novel AD therapeutics. Reporting procedures may include directly contacting the applicable pharmaceutical company and/or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. Submission of adverse event data to ALZ-NET does not satisfy any other regulatory requirements for reporting. Participating sites should report all serious adverse events judged by the investigator to be possibly, probably, or definitely related to the compound of interest to the applicable pharmaceutical company (Marketing Authorization holder) within 24 hours of becoming aware of the event. ALZ-NET will not be reporting adverse events in real-time (within 24 hours of the event), so it is required that participating sites follow the standard procedures for reporting.

All SAE reports should be submitted to the Institutional Review Board (IRB) of Record per their policies, procedures, and risk determination regarding AE reporting.

17.0 DATA PROTECTION, ACCESS, and QUALITY ASSURANCE

17.1 Data Privacy

Information about study patients will be kept confidential and managed according to applicable federal, and local laws, rules and regulations applicable to the institution, including but not limited to regulations of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and ICH Good Clinical Practices. Protected Health Information detailed in the ALZ-NET case report forms will be stored on secure servers at the American College of Radiology (ACR) and used to request healthcare claims data from applicable health insurance providers, and facilitation of optional components of the informed consent if agreed to by the patient. Authorization of PHI collection and limited use is outlined and agreed to by every ALZ-NET patient via the signed IRB-approved Informed Consent Form.
The electronic data files used for analysis will contain only study identification (ID) numbers and no identifying information. Neither patient's name nor other identifying information will be revealed in any reports or publications that arise from this research. All study data will be coded. All study documents will be identified by a unique study ID. The unique study ID will be linked to patient identifiers via a master code or key. Access to the master code/key will be limited to authorized ACR staff and to the site where the patient was enrolled. The master code/key that links study data to identifiers will be stored separately from the study data and remain protected.

Several components of data collection must be considered at each phase of the data life cycle. These include security, detection of bias, and quality assurance. The ACR has a robust security program based on the NIST 800-53 controls and experience working within a variety of regulatory frameworks based on the area of business (e.g., clinical research, registries, accreditation). Leveraging outsourced security vendors and in-house resources, the ACR remains in compliance with regulations, including HIPAA and 21 CFR Part 11 Compliance, and industry standards. The ACR also tailors and implements controls to

meet project requirements as necessary through each phase of the data life cycle. ACR maintains Policies and SOPs on areas including but not limited to Information Security, Access Control, Acceptable Use, Password Policy, Data Sanitization and Disposal, Information Classification, System Development Lifecycle, Data Backup, and Disaster Recovery. Policies and SOPs are reviewed biennially and require staff training. Similarly, validation and quality checks are laced throughout the data collection process, from design through archival.

After data are extracted, they are de-identified per Section 164.514(a) of the HIPAA Privacy Rule which provides the standard for de-identification of protected health information. Under this standard, health information is not individually identifiable if it does not identify an individual and if the covered entity has no reasonable basis to believe it can be used to identify an individual.

ACR TRIAD and ACR CONNECT's built in de-identification functionality is highly customizable to meet the wide range of projects that require differing levels of de-identification. At its core, this de-identification functionality allows ACR to conform to DICOM PS3.15, Chapter E, Application-Level Confidentiality Profile and Options, as a de-identifier. Due to the highly flexible rule sets and functionality of ACR de-identification, ACR staff creating the de-identification profile follow Table E.1-1 Application-Level Confidentiality Profile Attributes in DICOM PS3.15 Chapter E to claim this conformance for their individual de-identification profile implementation.

17.2 Data Access and Publication Policy

Authorized staff from collaborating ALZ-NET partners will have access to ALZ-NET data for the purpose of completing ALZ-NET related responsibilities and objectives. Any data being transferred to complete obligated responsibilities is covered under a comprehensive legal agreement to ensure privacy and security of data. The Brown University Statistical Center will serve as the statistical center for ALZ-NET and will have access to de-identified case report forms in the study database for statistical analyses and ongoing study reports. Brown University may also receive limited identifiable data to facilitate their obligations as an ALZ-NET partner.

Patients in ALZ-NET have the option to provide additional consent to be contacted for participation in future research opportunities. Patients that provide their additional consent to this optional component

give permission for their patient identifiable data (contact information) to be provided to TrialMatch®, a service offered by the Alzheimer's Association that assists interested parties in finding appropriate clinical trials. TrialMatch® will only contact consenting patients regarding studies that have been approved by a committee of ALZ-NET investigators and collaborators. These approved studies will add to the body of knowledge about dementia, especially when combined with information collected by ALZ-NET itself.

While none of the approved studies are an official part of ALZ-NET and the ALZ-NET project team has no influence over their procedures, all the studies are complementary to the goals of ALZ-NET. The ALZ- NET coordinating center will prepare Excel spreadsheets listing the names, addresses, telephone numbers, e-mail addresses and referring clinicians' names for every patient who indicated an interest in being contacted about additional research. The list will also indicate whether the patient signed the consent form himself or herself, as TrialMatch® agents may need to speak with a person authorized to make medical decisions instead of speaking directly with the patient. The Excel spreadsheets will be encrypted and placed on the ACR dropbox for TrialMatch® staff to retrieve. Passwords to open and decrypt the files will be sent separately from the dropbox link. ACR staff will delete the files from the dropbox after TrialMatch® staff have retrieved them. TrialMatch® staff will return the spreadsheets using the ACR dropbox with indicators showing which patients no longer wish to be contacted.
An essential goal of ALZ-NET (Aim 4) is to produce a data resource for the Alzheimer's disease research community-at-large. ALZ-NET will be open to and encourage the responsible sharing of de-identified

data collected during this project. ALZ-NET will be cooperating with external groups to make de-identified data, via safe-harbor standards, available to the Alzheimer's disease research community.

However, no part of the results of ALZ-NET obtained under this protocol, nor any information provided to the investigator for the purposes of participating in ALZ-NET, will be published or passed on to any third party without the consent of ALZ-NET leadership.

Any investigator involved in ALZ-NET is obligated to provide ACR with complete test results and all clinical data obtained from the patients in this protocol. Investigators will follow the ALZ-NET Data Access and Publication Policy posted at the ALZ-NET website. This policy provides information and guidelines on how to request access to clinical and imaging data and biorepository data or biological samples archived during ALZ-NET. No data will be transferred without a comprehensive Data Use Agreement in place between the ACR and the requesting party.

17.3 Quality Assurance and Record Retention

A goal of data monitoring is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the data management team and statistical center staff will apprise the study team listed on the protocol cover page who will then work with the site until the problem has been resolved.

FDA and ACR regulations require that all records related to human subject research be retained by the institution and Investigator for at least 2 years after the completion of the research. Records should be kept in either printed or electronic forms and be readily accessible for inspection at reasonable times [21.CFR.312.62(c)]. The ACR requires that each institution and investigator participating in ALZ-NET retain all records to meet DHHS, institutional, IRB, state and federal requirements.

18.0 CONFLICT OF INTEREST

Any ALZ-NET investigator or advisor who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by ACR policy) must fully and promptly disclose the nature of the conflict of interest to the ACR.

19.0 STATISTICAL CONSIDERATIONS

19.1 Overview

ALZ-NET engages providers who enroll patients and organizes the collection of data, images and specimens as described in this protocol. In this section we provide a concise overview of the statistical considerations for the analysis of the core set of data elements ALZ-NET collects directly on all patients. An overarching objective of ALZ-NET is to serve as a platform for (a) combining data from observational and/or randomized studies designed to address focused questions about specific AD treatments and (b) launching new hypothesis-driven, observational or randomized studies that are focused on the utilization and outcomes of specific AD treatments. The design and analysis of these new studies to be conducted in the ALZ-NET platform will be guided by specifically developed complete study protocols. The feasibility of such studies will depend crucially on the availability of an adequate patient cohort within ALZ-NET, with the necessary assessments to address study aims.

19.2 Analysis and Reporting of Data Collection Progress

The analysis of the core ALZ-NET data will routinely assess patterns of the accrual of patients and clinicians in ALZ-NET and progress in the data collection. A series of regular reports for administrative and scientific purposes will be established and augmented by ad-hoc reports for special purposes.

For patients, study reports will use graphs and tables to describe cross sectional and longitudinal

information collected by the referring sites and including;

- Socio-demographic and geo-spatial information
- Insurance and access to health care information
- Social determinants of health (SODH) characteristics
- Clinical characterization, cognitive and functional scale characteristics
- Reports from imaging (Amyloid PET, MRI, Tau) assessments
- Medication (AD and concomitant) prescribing and use
- Adverse events (including SAE and ARIA)
- Hospitalizations and ER visits
- Characteristics of participating sites and health care providers

For participating clinicians, study reports will describe practice setting, subspecialty training and board certifications, and experience in AD care including experience with novel AD therapies.

19.3 General Methods for Process of Care and Outcomes Analysis

In the initial period of ALZ-NET operations, the analysis of the core data set will be primarily descriptive and focused on the progress in patient enrollment and the collection and completeness of patient information. As the patient cohort grows, the focus of the analysis will be expanded to include the assessment of process of AD care and of patient outcomes.

19.3.1 Process of Care Analysis

a. Cross-sectional assessments of process of care will examine differences in care across patient subgroups defined by characteristics of individual patients, care settings, and geographic location. An important class of such studies will examine disparities in care across racial and ethnic subgroups of patients. The analysis of process of care studies will utilize multivariate regression modeling, often with a hierarchical or mixed model structure to account for relevant clustering. For hypothesis-driven, focused studies, propensity scores and matching may be utilized. As noted at the beginning of this section, such hypothesis-driven research will typically involve the development of a specific protocol that will rely on the current document for description of the general data collection and will include specific aims and statistical and sample size considerations tailored to the question at hand.

b. Longitudinal studies of process of care will examine the evolution of patterns of care over time, overall and for patient subgroups defined by patient characteristics, care settings, and geographic location. The analysis will utilize longitudinal regression modeling of data at various levels of aggregation.

19.3.2 Patient Outcome Analysis

The observational nature of registry data will be a fundamental consideration in any analysis examining the link of process of care to patient outcomes. It is envisioned that studies of outcomes from AD therapies will typically involve the development of specific protocols that are tailored to the therapies involved.

As many of the patient outcomes will involve longitudinal measurements in cognitive and functional scales, their analysis will rely on longitudinal regression modeling. In particular such models will be used to evaluate the relation of outcomes to baseline characteristics of the patients including demographics, co-morbidities and clinical features. In situations where it is possible to assess and characterize composite outcomes describing disease severity, time-to-event analysis will be used, and the results will be presented graphically via the corresponding cumulative incidence curves. The analysis will account for censoring and will use methods from survival analysis for outcomes defined by a single event or from multi-state modeling for assessing the duration of stay of a patient at particular disease stages. Comparisons among patient groups may involve matching by propensity score or other methods, as well as other approaches from causal inference.

19.3.3 Missing Data

The completeness of the data will be monitored routinely during the operation of the registry and the extent of missingness in key variables will be included in data progress reports. Important patterns will be identified, and determinations of potential remedial action will be made. For example, if unusually large percentages of missing data from individual sites are flagged, it may be possible to recover the information by contacting the sites involved. However, the prevention of missingness may be difficult to achieve in the registry setting.

The extent of missing data in response or explanatory variables will be assessed at the beginning of each analysis and patterns of missingness will be identified. Multiple imputation will be used as the common approach for handling missing data in ALZ-NET analysis.

20.0 REFERENCES

1. *Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2024. Alzheimers Dement (N Y). 2024 Apr 24;10(2):e12465. Dutch. doi: 10.1002/trc2.12465. PMID: 38659717; PMCID: PMC11040692.*
2. Alzheimer's Association. (2024), 2024 Alzheimer's disease facts and figures. Alzheimer's Dement., 20: 3708-3821. https://doi.org/10.1002/alz.13809
3. Rajan KB, Weuve J, Barnes LL, McAninch EA, Wilson RS, Evans DA. Population estimate of people with clinical AD and mild cognitive impairment in the United States (2020-2060). Alzheimers Dement 2021; doi:10.1002/alz.12362. Online ahead of print.
4. Guerreiro R, Bras J. The age factor in Alzheimer's disease. Genome Med 2015; 7:106.
5. McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R., Jr., Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N., Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S. and Phelps, C.H. (2011), The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, 7: 263-269. https://doi.org/10.1016/j.jalz.2011.03.005
6. Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B. and Phelps, C.H. (2011), The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, 7: 270-279. https://doi.org/10.1016/j.jalz.2011.03.008
7. Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., Iwatsubo, T., Jack, C.R., Jr., Kaye, J., Montine, T.J., Park, D.C., Reiman, E.M., Rowe, C.C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M.C., Thies, B., Morrison-Bogorad, M., Wagster, M.V. and Phelps, C.H. (2011), Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, 7: 280-292. https://doi.org/10.1016/j.jalz.2011.03.003
8. (2021), 2021 Alzheimer's disease facts and figures. Alzheimer's Dement., 17: 327-406. https://doi.org/10.1002/alz.12328
9. Leqembi Prescribing Information, (2023). Retrieved from https://www.leqembi.com/-/media/Files/Leqembi/Prescribing-Information.pdf.
10. Aduhelm Prescribing Information, (2021). Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761178s007lbl.pdf

Appendix A - ALZ-NET Affiliated CED Study

Study Title: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease Following Appropriate Use Recommendations in a Medicare Population: A Coverage with Evidence Development Study

NCT#: 06170268

I. BACKGROUND

Alzheimer's disease (AD) is the most common neurodegenerative disorder, associated with brain deposition of extracellular beta-amyloid (amyloid plaques) and intracellular tau (neurofibrillary tangles). It causes progressive cognitive impairment, especially memory loss, and is invariably fatal. AD is the most common cause of dementia, accounting for an estimated 60% to 80% of cases.[1] Patients with mild cognitive impairment (MCI) due to AD show evidence of decline in cognition from baseline and perform in the impaired range on objective cognitive tests, but are still independent in performing daily life activities. Patients with dementia due to AD show cognitive decline that renders them no longer independent in daily function. Dementia due to AD is further broken down into the stages of mild, moderate, and severe, which reflect the degree to which symptoms interfere with one's ability to carry out everyday activities.

Treatments that slow disease progression for AD have for the first time received regulatory approval.[2] These treatments are currently approved for patients in the MCI or mild dementia stage of AD and require confirmation of elevated brain amyloid. As more targeted therapies enter clinical practice, conceptual alignment between industry, academia, and clinicians around biomarker classification, AD diagnosis, and biologically based staging of AD will be highly relevant.

Clinical studies - both interventional and longitudinal - suggest that the underlying biological changes occur 10 to 20 years prior to the onset of clinical symptoms. As the disease progresses, cognitive and functional impairments and behavioral changes become more pronounced. AD is a complex disease process involving several biological mechanisms that interplay with each other - including amyloid plaques, tau tangles, metabolic mechanisms, cellular homeostasis, neuroinflammation, synaptic plasticity, as well as many other intersecting biological contributors. The presence of AD pathophysiology (i.e., amyloid plaques and tau tangles) in patients with MCI or dementia can be established using biomarkers, including established CSF assays and PET radiotracers and emerging plasma assays for beta-amyloid and phosphorylated tau.

In recent years, the U.S. Food and Drug Administration (FDA) has approved amyloid lowering monoclonal antibodies (anti-amyloid mAbs) for the treatment of AD. In 2021, the Alzheimer's Association recognized an urgent, unmet need to provide a cohesive and integrated strategy for real-world data (RWD) collection and real-world evidence (RWE) generation in real-world settings for all newly approved AD treatments to accelerate research and clinical advances. The FDA defines (RWD) as data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWD include data derived from electronic health records, medical claims data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status. RWE is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.[3] Building off the success of the Imaging Dementia - Evidence for Amyloid Scanning (IDEAS) and New IDEAS studies, the Association and its partners the American College of Radiology (ACR), American Society of Neuroradiology (ASNR), the Department of Biostatistics, Brown University School of Public Health, , and the

Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) project team which brought together over 25 study investigators and advisors to launch ALZ-NET as an integrated research and care network for all communities supported by real-world data (RWD) collection.[4] This first of its kind, voluntary provider-enrolled patient registry is a multi-site network collecting and archiving longitudinal, regulatory-grade patient data including but not limited to: demographic, medical history, neurologic, cognitive, functional, genetic, imaging, fluid biomarkers, treatment type/duration and safety data. ALZ-NET enrolls patients being evaluated for or treated with novel AD treatments approved by the FDA, including treatments that slow disease progression, address cognition/function, or address neuropsychological/ behavioral symptoms.[5] ALZ-NET is currently tracking the resource utilization and health outcomes of such patients. As of November 2023, ALZ-NET includes 23 active sites with over 60 enrolled participants and over 140 clinical sites in various stages of the startup process. Additionally, ALZ-NET is recommended in the FDA prescribing information for two recently approved monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease, encouraging both clinicians and patients to participate in the network. ALZ-NET is also designed to work collaboratively and in conjunction with affiliated studies conducted by academia, industry, federal or ALZ-NET project teams. Many affiliated studies may have unique or expanded data collection needs; however, affiliated studies will be able to leverage the provider-reported ALZ-NET minimum data set for analyses with the goal of aligning both consent and data collection efforts to minimize patient and site burden.

II. SCOPE

This protocol describes the 'ALZ-NET Affiliated Study: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease Following Appropriate Use Recommendations[6] in a Medicare Population: A Coverage with Evidence Development Study' (henceforth 'ALZ-NET Affiliated CED Study'). This is the first of ALZ-NET's affiliated studies that utilizes the infrastructure of the national ALZ-NET provider-enrolled patient registry protocol (henceforth 'ALZ-NET Protocol') to either capture additional information according to affiliated study needs or conduct specific and detailed analysis on ALZ-NET Protocol data. This national CED study is designed to further observe and collect data on longitudinal cognition, function and safety of amyloid lowering mAbs that have received traditional FDA-approval in AD patients over the course of the treatment period and beyond. The principal purpose of the ALZ-NET Affiliated CED Study is to study the long-term effectiveness and safety of these new treatments and whether these treatments improve the participants' health outcomes. Therefore, the over-arching goals of ALZ-NET are directly aligned with the CED questions posed in the National Coverage Decision for this class of therapies.

This protocol for a prospective human research study will be conducted in compliance with and according to United States and International Conference on Harmonization Good Clinical Practice Guidelines, applicable government regulations (e.g., Title 45, Part 46 Code of Federal Regulations), standards of scientific integrity (i.e. ICMJE and Agency for Healthcare Research and Quality), and the American College of Radiology (ACR) research policies and procedures. See *Section 6.4 Single Institutional Review Board (IRB) of Record, Section 10.0 Patient Consent, Eligibility and Registration, Section 11.1 Clinical Data Submission*, and *Section 17.0 Data Protection, Access, and Quality Assurance* of the ALZ-NET Protocol for more details. The ALZ-NET Affiliated CED Study protocol will be registered on ClinicalTrials.gov by the study sponsor once CMS approves the protocol.

The ALZ-NET Affiliated CED Study is sponsored by the Alzheimer's Association, managed and operated by the American College of Radiology (ACR), and directed by the Centers for Medicare & Medicaid Services (CMS). See *Section 6.0 ALZ-NET Leadership and Organizational Structure* of the ALZ-NET Protocol for more details.

In order to meet the specific aims and objectives of the ALZ-NET Affiliated CED Study, the participating site and clinician network established by the ALZ-NET Protocol will be leveraged. The sites enrolled in ALZ-NET must meet specific criteria that demonstrate clinical expertise and infrastructure to provide

treatments consistent with the safety monitoring outlined in the FDA-approved prescribing information. ALZ-NET collects site and staff data to ensure participation of multidisciplinary dementia teams and optimal medical management. See *Section 7.0 Participating Site Registration Requirements, Section 8.0 Site Investigator Requirements,* and *Section 9.0 Site Staff Requirements* of the ALZ-NET Protocol for details.

III. PATIENT POPULATION AND ELIGIBILITY

Patients that are included in the ALZ-NET Affiliated CED study must first be enrolled into the ALZ-NET Protocol by a participating and active site. Eligibility and enrollment into the ALZ-NET Protocol is broader and encompasses the population analyzed by the ALZ-NET Affiliated CED Study. For greater detail of the ALZ-NET Protocol's eligibility criteria and enrollment process, please see *Section 10.0 Patient Consent, Eligibility, and Registration*. Enrollment into the ALZ-NET Protocol ensures that patients who are treated with traditional FDA-approved anti-amyloid mAb are being treated and cared for in a real-world clinical setting and in alignment with FDA prescribing information as well as the published Appropriate Use Recommendations.[6]

Cohort Inclusion Criteria for ALZ-NET Affiliated CED Study:

1. Enrollment into the ALZ-NET Protocol;
2. Medicare beneficiary with primary insurance of Medicare Part B (traditional Medicare) or Part C (Medicare Advantage plan). Dual-eligible Medicaid coverage also allowable;
3. Clinical diagnosis of MCI due to AD or mild AD dementia, both with confirmed presence of amyloid beta pathology consistent with AD;
4. Being treated with a beta-amyloid targeting monoclonal antibody that has received traditional (i.e., full) FDA approval for the treatment of Alzheimer's disease

Defining the CED population

Any patient that consents to be a part of the ALZ-NET Protocol and meets the CED cohort inclusion criteria listed above will have their data automatically included in analyses for the purposes of this ALZ-NET Affiliated CED Study. If a patient meets the CED cohort inclusion at any point during their participation in ALZ-NET, their data may be incorporated into the CED Study cohort. If a patient terminates their Medicare coverage while participating in ALZ-NET or stops treatment with a traditional FDA-approved anti-amyloid mAb, the patient will remain within the CED analysis cohort.

Individuals of all genders, and from all ethnic groups are eligible for this study. The ALZ-NET program, inclusive of this ALZ-NET Affiliated CED Study, is committed to ensuring the inclusion of a population whose diversity of patients is representative of the national population with MCI due to AD or mild AD dementia. Eligibility criteria for ALZ-NET and the ALZ-NET Affiliated CED Study do not create additional barriers for traditionally underrepresented populations. Therefore, the study expects to produce results that are generalizable to the Medicare population. ALZ-NET aims to increase access to this study through the development of a robust national network of participating sites. The sites participating in ALZ-NET are primarily recruited through the existing IDEAS and New IDEAS Study networks.[7,8,9,10] These sites are located across the entire United States, and the New IDEAS study team in particular has experience operating AD-related CED studies with a focus on recruitment of traditionally underrepresented populations. As of September 2023, the New IDEAS Study has enrolled over 5,000 individuals, with over 2,200 individuals who self-identify as Black/African American and/or Hispanic/Latinx, representing 45% of the total enrolled study cohort. The ALZ-NET Affiliated Study will leverage resources of the New IDEAS Study and the ALZ-NET partnering organizations to consistently educate participating sites on frequently cited barriers to minority participation in clinical trials.[11,12,13] Also see *Section 2.0 Introduction* and *Section 3.0 Scope of ALZ-NET* of the ALZ-NET Protocol for more

details.

Based on sample size considerations, this ALZ-NET Affiliated CED Study aims to include at least 20,000 eligible patients per drug that has received traditional FDA-approval as a mAb directed against amyloid for Alzheimer's disease.

Defining the comparator population

The ALZ-NET Affiliated CED Study will use a comparator population to address the questions poised. This population will be derived from historical normative data from several sources. We will rely on longitudinal data from observational natural history study cohorts that include individuals diagnosed with biomarker confirmed MCI due to AD and mild AD dementia who have never initiated FDA-approved anti-amyloid mAbs (treatment naïve). We will use data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the National Alzheimer's Coordinating Center (NACC) which houses data from the NIA-funded Alzheimer's Disease Research Centers (ADRCs). There are two large-scale, multi-site observational studies of AD with broad geographic representation across the U.S. ADNI has a well-defined clinical and biomarker data collection processes.[14] NACC data is organized using the Uniform Data Set (UDS), using a prospective, standardized, and longitudinal clinical evaluation of the subjects in the National Institute on Aging's ADRC Program. Collectively, ADNI and NACC include the necessary cognitive and functional assessments for appropriate analyses (MMSE/MoCA, FAQ, NPI-Q).[15] We will identify a comparator population from ADNI and NACC that are matched to the treated group enrolled in the ALZ-NET Affiliated CED study by key demographic (e.g., age, sex, race/ethnicity, years of education) and clinical (e.g., medical comorbidities, disease stage (MCI/dementia), baseline MMSE/MoCA, use of AD symptomatic medications, APOE genotype) features.

IV. STUDY DESIGN AND OBJECTIVES

The proposed ALZ-NET Affiliated CED Study protocol, inclusive of a specific CED analysis plan, is implemented as an appendix to the ALZ-NET parent registry protocol to meet the NCD requirements. The ALZ-NET Affiliated CED Study design and objectives are appropriate to answer the research questions being asked in the CED requirements. This study aims to further evaluate traditional FDA-approved anti-amyloid mAb treatments by collecting RWD in a broader Medicare beneficiary population across a variety of clinical practice settings. Data elements and collection procedures for the ALZ-NET Affiliated CED Study mirrors that of which is collected as part of the ALZ-NET protocol.

Longitudinal data being collected about enrolled ALZ-NET patients, inclusive of those who are part of this CED analysis include but are not limited to: patient demographics and characteristics; medical history; lifestyle data; vital signs; clinical features of co-pathology; cognitive and functional assessments; concomitant medications; Alzheimer's disease diagnosis and diagnostic testing; clinical events; imaging; healthcare encounters; adverse/serious adverse events; and ARIA events.

The following data elements associated with patient and practice characteristics will be key for addressing the objectives of this ALZ-NET Affiliated CED Study protocol including, but not limited to, age; sex/gender; race/ethnicity; education level; diagnosis (MCI vs early dementia); baseline and longitudinal Montreal Cognitive Assessment (MoCA), Mini Mental State Examination (MMSE), Functional Activities Questionnaire (FAQ) scores, Neuropsychiatric Inventory Questionnaire (NPI-Q); concomitant medications (e.g. symptomatic AD medications and anti-thrombotic medications); comorbidities (e.g. stroke, hypertension, diabetes); APOE genotype; clinical features of co-pathology; healthcare encounters; adverse/serious adverse events; ARIA events and clinical setting (e.g. office based vs hospital/medical center). See *Section 11.0 ALZ-NET Design & Data Procedures* and *Section 12.0 ALZ-NET Data Elements, ALZ-NET Summary Table of Data Elements,* and *Section 13.0 Health Insurance Claims Data*

of the ALZ-NET Protocol for all data elements collected and more details. In particular, *Section 12.8 Additional Measures (Cognitive, Functional, and Behavioral)* describes the Additional Measures form which must be submitted at the baseline and follow-up time points for all registered patients via one of ALZ-NET's available data transfer mechanisms. Additionally, *Section 12.14 Image Assessment, Section 12.15 AD Treatment and Dosing, Section 12.16 Healthcare Encounters (Hospitalizations and ER Visits)* and *Section 12.17 Adverse Events (AEs)/Amyloid Related Imaging Abnormalities (ARIA) Events* discuss forms that will be required to capture important information associated with safety and tolerability of the individual medications. ALZ-NET will collect raw images in DICOM format and the accompanying imaging report through TRIAD/CONNECT (see *Section 14.0 Imaging Considerations*) to support thorough evaluation and confirmation of ARIA related events in the treatment population. This information will be key in tracking legitimate safety outcomes for known side effects associated with anti-amyloid treatment.

Defining the length of follow up for CED data collection and analysis:

For this ALZ-NET Affiliated CED Study, historical matched controls (ADNI and NACC) will be compared to data collected and analyzed for each patient, for each traditional FDA-approved anti-amyloid mAb, at baseline and longitudinally over a span of 2 years from treatment initiation, even if treatment is terminated within that time period. Data entry time points occur at Baseline (BL), 6 months, 12 months, 18 months, 24 months, and annually thereafter (see *Section 11.0* of the ALZ-NET Protocol for more details). This is longer than data collection for recent Phase 3 confirmatory trials for these types of treatments which were 18 months in duration. Based on Phase 3 data, prescribing information, and peer-reviewed publications for this class of therapeutics, increased clinical vigilance is necessary within the first 6 months of initiating treatment to monitor for ARIA and other side effects.[6,16,17,18] The primary endpoint analyses for the CED will be assessed at, the 2-year follow up time point for both the treatment and the control arms. The two-year time frame will include 3 datapoints (baseline, 12 months and 24 months) from the comparator group. Beyond this, individuals in the treatment arm will continue to be followed in perpetuity as part of the ALZ-NET protocol, until a participation end point is met. As long as an enrolled patient continues to receive care from a participating ALZ-NET provider, and does not withdraw their consent to participate, ALZ-NET will continue to collect data. A patient's participation in ALZ-NET can be terminated by one of the following ways: withdrawal of consent, meeting the ALZ-NET definition of Lost to Follow-Up, death, closure of ALZ-NET, or termination of the current provider site's participation in ALZ-NET (see *Section 11.8* of ALZ-NET Protocol for more details).

Aims and Objectives:

The ALZ-NET Affiliated CED Study has developed specific objectives to address the CED questions set forth by the Centers for Medicare and Medicaid Services (CMS). The objectives below address specifically the CED study requirements, the outcomes and measures used to answer each question. The methodology for analysis is detailed in Section V below.

- Does the anti-amyloid mAb meaningfully improve health outcomes (i.e., slow the decline of cognition and function) for patients in broad community practice?
- Do benefits, and harms such as brain hemorrhage and edema, associated with use of the anti-amyloid mAb, depend on characteristics of patients, treating clinicians, and settings?
- How do the benefits and harms change over time?

Objective #1: Evaluate whether traditional FDA-approved anti-amyloid mAb treatments improve health outcomes (as measured by slowing of cognition and function) over time in a real-world Medicare beneficiary population in broad clinical settings (treatment arm) compared to matched historical controls

drawn from a treatment naïve population (control arm).

Outcomes: The study will compare longitudinal change in cognition and function between the two arms. Control subjects from ADNI/NACC will be matched to ALZ-NET participants by key demographic (e.g., age, sex, race/ethnicity, years of education) and clinical (e.g., medical comorbidities, disease stage (MCI/dementia), baseline MMSE/MoCA, use of AD symptomatic medications, APOE genotype) features. The key comparison outcomes (collected in both ALZ-NET and ADNI/NACC) will be change in: (1) MMSE/MoCA (cognition); (2) FAQ (function); (3) NPI-Q (neuropsychiatric symptoms).

Additionally, *within ALZ-NET* participants, we will assess the relationship between longitudinal change in clinical outcomes (MMSE/MoCA, FAQ, NPI-Q) and baseline patient characteristics (e.g. age, sex/gender, race/ethnicity, education level, Area Deprivation Index[19] (ADI), diagnosis (MCI vs early dementia), baseline MMSE/ MoCA, FAQ, and NPI-Q scores; concomitant medications (e.g. symptomatic AD medications and anti-thrombotic medications), comorbidities (e.g. stroke, hypertension, diabetes), APOE genotype, clinical features of co-pathology and practice characteristics (e.g. office based vs hospital/medical center).

Outcome Measures: The primary measures of cognitive status will be the overall scores of MoCA or MMSE. The primary measure of functional status will be the overall FAQ score. Secondary and exploratory analyses will evaluate longitudinal change in the NPI-Q (measures neuropsychiatric symptoms).

Objective #2: Evaluate safety outcomes of traditional FDA-approved anti-amyloid mAb treatments over time in a real-world Medicare beneficiary population in broad clinical settings.

Outcomes: Describe longitudinal adverse events in patients treated with anti-amyloid monoclonal antibodies, and their relationship to baseline patient characteristics (e.g. age, sex/gender, race/ethnicity, education level, Area Deprivation Index (ADI), diagnosis (MCI vs early dementia), baseline MMSE/MoCA and FAQ scores, concomitant medications (e.g. symptomatic AD medications and anti-thrombotic medications), comorbidities (e.g. stroke, hypertension, diabetes), APOE genotype, clinical features of co-pathology and practice characteristics (e.g. office based vs hospital/medical center).

Outcome Measures: The measures of safety and health outcomes will be summaries of rates of adverse events over time. Specific safety outcomes of interest such as ARIA (classified as *mild* or *moderate-severe* and also as *asymptomatic* or *symptomatic*) will be modeled according to fixed and time-varying characteristics associated with treatment.

Data Access and Publication:

An essential goal of ALZ-NET is to produce an invaluable data resource for the Alzheimer's disease research and clinical community at large. ALZ-NET will be open to and encourage data sharing of the data resources collected by the network. ALZ-NET plans to make its data publicly accessible on an ongoing basis throughout the duration of the project. Data of patients included in the ALZ-NET Affiliated Study will be included in the publicly accessible de-identified data set and able to be used by external researchers as described in the protocol's *Section 17.0 Data Protection, Access and Quality Assurance.*

ALZ-NET Affiliated CED Study is committed to a public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or the study is terminated early. The results of the study will be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, the initial release may be an abstract that will meet the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). In that event, a full report of the outcomes will be made public no later than 3 years after the end of data collection.

V. ANALYSIS PLAN

The analysis of the longitudinal data in the treatment arm and the corresponding data in the control arm of the study will address the primary questions regarding real-world effectiveness of the therapy in comparison to experience from historical controls. In addition, the longitudinal analysis of the full dataset from patients in the treatment arm will provide critical preliminary RWD for both short and long-term patient-oriented outcome measures associated with cognition, function, and safety. In this study, data on (I) patient cognitive and functional status, and (II) adverse events from therapy will be collected at baseline and longitudinally over a span of up to 2 years from treatment initiation. This cohort will be compared to historical matched controls from ADNI and NACC data who are treatment naïve. Patients in the control arm will be matched to those in the therapy arm on the basis of key demographics (e.g., age, sex, race/ethnicity, years of education) and clinical features (e.g., medical comorbidities, disease stage (MCI/dementia), baseline MMSE/MoCA, use of AD symptomatic medications, APOE genotype). The analysis of these data will respond to the three key CED requirement questions 1) Does the anti-amyloid mAb meaningfully improve health outcomes (i.e., slow the decline of cognition and function) for patients in broad community practice?, 2) Do benefits, and harms such as brain hemorrhage and edema, associated with use of the anti-amyloid mAbs, depend on characteristics of patients, treating clinicians, and settings?, and 3) How do the benefits and harms change over time?

Assessment of therapy effectiveness (Objective #1)

The primary measures of cognitive status will be the overall scores of MoCA or MMSE. The primary measure of functional status will be the overall FAQ score. Additional clinical scales (NPI-Q) will also be examined in secondary analyses.

The *primary goal* of the analysis will be the *comparison of response to therapy* in the treatment to the control arm. After graphical exploration of the data, the confirmatory analysis will be based on longitudinal regression modeling of each response. The analysis will focus on the association of the response with therapy status, controlling for characteristics of the patients fixed at baseline, such as demographics and clinical features (medical co-morbidities, disease stage (MCI/dementia), baseline MMSE/MoCA, use of AD symptomatic medications (i.e., cholinesterase inhibitors and memantine), and APOE genotype). Interaction terms of therapy status with covariates will also be included in the model. Spline models will be employed for the response variable.

A *major additional goal* of the analysis will be the detailed *assessment of the longitudinal course* of patients receiving therapy. Graphical displays of the longitudinal course of each scale will be constructed and examined to determine possible patterns in patient trajectories. In further exploration of these trajectories, we will use tree-structured, mixed effects regression modeling to identify potential subsets of patients as defined by baseline characteristics (e.g. age, sex/gender, race/ethnicity, education level, Area Deprivation Index (ADI), diagnosis (MCI vs early dementia), baseline MMSE/MoCA and FAQ scores, concomitant medications (e.g. symptomatic AD medications and anti-thrombotic medications), comorbidities (e.g. stroke, hypertension, diabetes), APOE genotype, clinical features of co-pathology) and practice characteristics (e.g. office based vs hospital/medical center).[20,21] A confirmatory analysis will be based on longitudinal regression modeling of each response. The analysis will assess the association of the response with covariates describing characteristics of the patients fixed at baseline, such as demographics, co-morbidities and clinical features, as well as time-varying characteristics. The latter could include indicators of compliance with the particular drug therapy, setting of care, and other salient variables. Spline models will be employed for the response variable. In an elaboration of the separate analysis of each response we will also consider joint modeling of the three primary measures and will examine the joint evolution of these measures over time.[22,23] Although the modeling approaches envisioned for the analysis could accommodate irregularly spaced observations, we expect a non-

negligible amount of missing data in response and explanatory variables. Multiple imputation will be the common approach for handling missing data, when the MAR assumption appears to be appropriate.

Assessment of therapy safety (Objective #2)

This analysis will be conducted using data from the treatment arm of the study. For exploratory purposes, safety data will be summarized and presented as time-varying (e.g. quarterly, semi-annually, annually) rates of adverse events over the full study period. These summaries will be constructed for the overall patient cohort as well as for various subsets defined by characteristics of interest (e.g. age, sex/gender, race/ethnicity, education level, Area Deprivation Index (ADI), diagnosis (MCI vs early dementia), baseline MMSE/MoCA and FAQ scores, concomitant medications (e.g. symptomatic AD medications and anti-thrombotic medications), comorbidities (e.g. stroke, hypertension, diabetes), APOE genotype, clinical features of co-pathology) and practice characteristics (e.g. office based vs hospital/medical center). Estimates of rates of adverse events will be presented alongside estimates of similar adverse events derived from reports of clinical trials.

For specific adverse events of high interest, we will utilize time-to-event models to examine the relation of characteristics of the patient and the setting of care to the occurrence of the event. For example, this analysis will be carried out for ARIA, classified as *mild* or *moderate-severe* and also as *asymptomatic* or *symptomatic*. The models will include covariates that are fixed in time, such as demographics, or time-varying, describing the course of therapy. To account for the presence of competing risks in this analysis we will estimate event-specific hazards.

Sample Size Considerations

Patients enrolled in the ALZ-NET Affiliated CED Study will be drawn from ALZ-NET and may continue in the registry beyond the observation period of 2 years envisioned in this CED protocol. Historical matched controls from ADNI and NACC will be used for analysis.

The following table presents sample sizes of the number of ALZ-NET study participants in the treatment arm and control patients needed to compare performance as measured by a marker of cognition or function. The sample size of treatment and control patients *with complete baseline and year 2 data* would be sufficient to provide the indicated power to detect an effect size (standardized difference of the two means) of the indicated magnitude between the arms using a test of level 0.025 to account for multiplicity for the two comparisons (cognition and function). Computations were performed using the Pass 2023 software.

Based on reported trial results an effect size of 0.25 appears appropriate as a target. However, we also considered a range of other values that may be realistic for a RWD setting. Because the availability of appropriate controls is expected to be more limited than the potential enrollment in the therapy arm, we chose a design with a larger sample size for the therapy arm.

We expect to be able to enroll at least **20,000** participants in the treatment arm over period of 2 years. Assuming conservatively that we will have *complete data* on 75% of these participants (that is, **15,000** patients), and that we will identify 573 historical control cases with complete data, the study will have 90% power to detect an effect of size as low at 0.15. The total length of the comparative study is estimated at 4 years, to allow for the 2-year response on all participants.

Power	Treatment SS	Control SS	Total SS	Effect Size
0.8	20000	998	21998	0.10
0.8	20000	432	20432	0.15
0.8	20000	241	20241	0.20
0.8	20000	154	20154	0.25
0.9	20000	1324	21324	0.10
0.9	20000	568	20568	0.15
0.9	20000	316	20316	0.20
0.9	20000	201	20201	0.25
0.8	15000	1015	16015	0.10
0.8	15000	435	15435	0.15
0.8	15000	242	15242	0.20
0.8	15000	154	15154	0.25
0.9	15000	1354	16354	0.10
0.9	**15000**	**573**	**15573**	**0.15**
0.9	15000	317	15317	0.20
0.9	15000	202	15202	0.25

VI. SUMMARY

The ALZ-NET Affiliated CED Study aims to directly align with the CED questions for CMS-approved studies of a monoclonal antibody directed against amyloid that has received traditional approval from the FDA. ALZ-NET will develop and implement the critical elements needed for the further observation of the use of amyloid lowering mAbs in real-world practice in Medicare beneficiaries to meet the requirements of CED. The ALZ-NET Affiliated CED Study protocol, an appendix of the parent ALZ-NET Protocol, details the multidisciplinary dementia leadership team and the study structure; site registration (including site investigator and site staff) requirements indicating expertise and infrastructure consistent with the safety monitoring outlined in FDA-approved labels; patient identification and consent processes that include a diverse and representative population; data elements that include instruments used to assess cognition and function, data collection, data protection, access and quality assurance procedures; and overall analysis plan and statistical considerations. The ALZ-NET Affiliated CED Study research plan, methodology and analysis plan address how the ALZ-NET registry can be used as the infrastructure to successfully carry out the aims proposed in this study. The ALZ-NET Protocol and Affiliated CED Study Appendix clearly addresses the standards listed as Medicare requirements for CED coverage.

ALZ-NET Affiliated CED Study and CMS Required Design Specifications

NCD Section	CMS Requirement	ALZ-NET CED
(B)(3)	For CMS-approved studies, the protocol, including the analysis plan, must include:	
	a. A study population whose diversity of patients are representative of the national population with MCI due to AD or mild AD dementia.	Yes. See section III, Patient Population and Eligibility.
	b. A neurocognitive evaluation and a description of the instruments used to assess cognition and function for the clinical diagnosis of MCI due to AD or mild AD dementia for study enrollment and outcomes assessment.	Yes. See section IV, Research Design and Objectives.
	c. A description of: i. The multidisciplinary dementia team and optimal medical management. ii. Study sites with clinical expertise and infrastructure to provide treatments consistent with the safety monitoring outlined in the FDA-approved label.	Yes. See section II, Scope
(B)(4)	CMS-approved studies of a monoclonal antibody directed against amyloid (anti-amyloid mAb) approved by FDA for the treatment of AD based upon evidence of efficacy from a direct measure of clinical benefit must address all of the questions below:	
	a. Does the anti-amyloid mAb meaningfully improve health outcomes (i.e., slow the decline of cognition and function) for patients in broad community practice? b. Do benefits, and harms such as brain hemorrhage and edema, associated with use of the anti-amyloid mAb, depend on characteristics of patients, treating clinicians, and settings? c. How do the benefits and harms change over time?	Yes. See section IV, Research Design and Objectives.
(B)(5)	CMS-approved studies must adhere to the standards of scientific integrity that have been identified by the Agency for Healthcare Research and Quality: *(Check box if all criteria are met in (a)-(m) checklist above)*	

	a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.	Yes. See section II, Scope.
	b. The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.	Yes.
	c. The research study does not unjustifiably duplicate existing studies.	Yes.
	d. The research study design is appropriate to answer the research question being asked in the study.	Yes.
	e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.	Yes. See section II, Scope
	f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must be in compliance with 21 CFR parts 50 and 56.	Yes. See section II, Scope
	g. All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).	Yes. See section II, Scope
	h. The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CED coverage.	Yes.
	i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.	Yes.
	j. The clinical research study is registered on the ClinicalTrials.gov Web site by the principal	Yes. See section II, Scope

	sponsor/investigator prior to the enrollment of the first study subject.	
	k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However, a full report of the outcomes must be made public no later than 3 years after the end of data collection.	Yes. See section IV, Research Design and Objectives.
	l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.	Yes. See section III, Patient Population and Eligibility.
	m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.	Yes. See section III, Patient Population and Eligibility.

VII. References:

1. Alzheimer's Association. (2024), 2024 Alzheimer's disease facts and figures. Alzheimer's Dement., 20: 3708-3821. https://doi.org/10.1002/alz.13809.
2. https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval, last accessed 9/28/2023.
3. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence, last accessed 9/28/23.
4. Rabinovici GD, Rafii MS, Apgar C, An N, Barakos J, Brangman SA, Daffner KR, Edelmayer RM, Gatsonis C, Hakim R, Hanna L, Jicha, GA, Jordan J, Lingler JH, Lopez OL, March A, Porsteinsson AP, Possin KL, Romero K, Salloway SP, Sano M, Sivakumaran S, Snyder HM, Stebbins P, Vukmir RB, Whitlow CT, Carrillo MC. ALZ-NET: Using Real World Evidence to Inform the Future of Alzheimer's Treatment and Care. Alzheimer's Dement., 18: e069542. Alzheimer's Association International Conference 2022. San Diego, CA.
5. https://www.alz-net.org/, last accessed 9/28/2023.
6. Cummings J, Apostolova L, Rabinovici GD, Atri A, Aisen P, Greenberg S, Hendrix S, Selkoe D, Weiner M, Petersen RC, Salloway S. Lecanemab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2023;10(3):362-377. doi: 10.14283/jpad.2023.30. PMID: 37357276; PMCID: PMC10313141.
7. https://www.ideas-study.org/Original-Study, last accessed 9/28/2023.
8. https://www.ideas-study.org/About-Us, last accessed 9/28/2023.
9. Rabinovici GD, Gatsonis C, Apgar C, Chaudhary K, Gareen I, Hanna L, Hendrix J, Hillner BE, Olson C, Lesman-Segev OH, Romanoff J, Siegel BA, Whitmer RA, Carrillo MC. Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia. JAMA. 2019 Apr 2;321(13):1286-1294. doi: 10.1001/jama.2019.2000. PMID: 30938796; PMCID: PMC6450276.
10. Wilkins CH, Windon CC, Dilworth-Anderson P, Romanoff J, Gatsonis C, Hanna L, Apgar C, Gareen IF, Hill CV, Hillner BE, March A, Siegel BA, Whitmer RA, Carrillo MC, Rabinovici GD. Racial and Ethnic Differences in Amyloid PET Positivity in Individuals With Mild Cognitive Impairment or Dementia: A Secondary Analysis of the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) Cohort Study. JAMA Neurol. 2022 Oct 3;79(11):1139–47. doi: 10.1001/jamaneurol.2022.3157. Epub ahead of print. PMID: 36190710; PMCID: PMC9531087
11. Dilworth-Anderson P, Cohen MD. Beyond diversity to inclusion: recruitment and retention of diverse groups in Alzheimer research. Alzheimer Dis Assoc Disord. 2010;24 Suppl:S14-18.
12. Dilworth-Anderson P, Thaker S, Burke JM. Recruitment strategies for studying dementia in later life among diverse cultural groups. Alzheimer Dis Assoc Disord. 2005;19(4):256-260.
13. Dilworth-Anderson, P. Introduction to the Science of Recruitment and Retention Among Ethnically Diverse Populations. Gerontologist. 2011:51(Suppl 1): S1–S4.
14. https://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/clinical/ADNI3_Protocol.pdf, last accessed 10/29/2023.
15. https://naccdata.org/data-collection/forms-documentation/uds-3, last accessed 10/29/2023.
16. Budd Haeberlein S, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, Dent G, Hansson O, Harrison K, von Hehn C, Iwatsubo T, Mallinckrodt C, Mummery CJ, Muralidharan KK, Nestorov I, Nisenbaum L, Rajagovindan R, Skordos L, Tian Y, van Dyck CH, Vellas B, Wu S, Zhu Y, Sandrock A. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimers Dis. 2022;9(2):197-210. doi: 10.14283/jpad.2022.30. PMID: 35542991.
17. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S,

Irizarry M, Kramer LD, Iwatsubo T. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023 Jan 5;388(1):9-21. doi: 10.1056/NEJMoa2212948. Epub 2022 Nov 29. PMID: 36449413.

18. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, Wessels AM, Shcherbinin S, Wang H, Monkul Nery ES, Collins EC, Solomon P, Salloway S, Apostolova LG, Hansson O, Ritchie C, Brooks DA, Mintun M, Skovronsky DM; TRAILBLAZER-ALZ 2 Investigators. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023 Aug 8;330(6):512-527. doi: 10.1001/jama.2023.13239. PMID: 37459141; PMCID: PMC10352931.
19. Kind AJH, Buckingham W. Making Neighborhood Disadvantage Metrics Accessible: The Neighborhood Atlas. *New England Journal of Medicine*, 2018. 378: 2456-2458. DOI: 10.1056/NEJMp1802313. PMCID: PMC6051533.
20. Eo, S. H., & Cho, H. (2014). Tree-structured mixed-effects regression modeling for longitudinal data. Journal of Computational and Graphical Statistics, 23(3), 740-760.
21. Gottard, A., Vannucci, G., Grilli, L. et al. Mixed-effect models with trees. Adv Data Anal Classif 17, 431–461 (2023). https://doi.org/10.1007/s11634-022-00509-3
22. Verbeke G, Fieuws S, Molenberghs G, Davidian M. The analysis of multivariate longitudinal data: A review. Statistical Methods in Medical Research. 2014;23(1):42-59. doi:10.1177/0962280212445834
23. Poulet P-E, Durrleman S. Multivariate disease progression modeling with longitudinal ordinal data. Statistics in Medicine. 2023; 42:3164–3183 DOI: 10.1002/sim.9770