ALZ-NET Protocol Synopsis

IRB Protocol Number / NCT Number	Pro00064645 / NCT: *TBD*
Protocol Version and Date	Version 2 - March 27, 2023
Title of Study	Alzheimer's Network for Treatment and Diagnostics (ALZ-NET)
Study Aims and Objectives	**AIM 1:** Establish the necessary registry infrastructure: ● Develop a database to gather regulatory grade, longitudinal data from patients being evaluated for and 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 develop mechanisms to co-enroll patients in affiliated trials **AIM 3**: The registry will collect data to evaluate long term safety, clinical use and outcomes: ● Characterize the patient population and physician prescribing patterns ● Track baseline and longitudinal cognitive and functional trajectories ● Assess patient management including initiation and duration of treatment ● Evaluate longitudinal safety and tolerability **AIM 4:** Merge 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
Background and Design	There are over 140 therapies being tested in clinical trials for Alzheimer's disease (AD) today. 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 or treated with novel FDA-approved AD therapy in real-world settings, to inform clinical practice.

	ALZ-NET will collect longitudinal clinical, imaging, and safety data for enrolled patients being evaluated for or 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 individuals from a variety of backgrounds and communities, to achieve representativeness beyond the populations historically enrolled in clinical trials. 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. **Patients who are being evaluated for, have already, or will be initiating treatment with an FDA-approved novel therapy for AD will be asked to enroll in ALZ-NET.** Treatments will be prescribed at the provider's discretion, and it is expected that prescribing clinicians follow FDA prescribing labels and published Appropriate Use Recommendations for novel FDA-approved therapies for AD. Novel FDA-approved therapies for AD are drugs that have received approval as treatments for Alzheimer's disease (AD) from the U.S. Food and Drug Administration since 2021. Patients will be monitored by the treating clinician according to patient needs and local standard of care (SOC). To achieve sufficient data for ALZ-NET, patients will be monitored throughout treatment duration, and following treatment 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. The table below provides a summary of data forms that will be collected as part of the ALZ-NET. 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 this and future treatments in the real world — in other words, outside of narrowly constrained clinical trials. It will collect longitudinal data through site submitted case report forms and payer claims from individuals that are appropriate for FDA-approved AD therapeutics, based on their label designation. In addition to the aims and objectives outlined within this protocol, ALZ-NET will serve as a backbone registry and platform for 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 receiving a novel FDA approved treatment for AD. This collaboration

	structure is designed to reduce the operational burden of participating sites and patients. Creation of a national voluntary, provider-enrolled, patient registry 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.
Patient Eligibility Criteria	**<u>Inclusion Criteria</u>** 1. Patient or patient's legally authorized representative (LAR) or proxy (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, 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.
Data Submission Process and 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. 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 at the applicable **follow-up data entry time points: 6 months; 12 months; 18 months; 24 months; Annually thereafter until a participation endpoint is met.**

	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. 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.
Study Centers and Investigators	The criteria to be considered a **site investigator**, otherwise known as a prescribing clinician: • Hold credentials that authorize the prescription of novel FDA-approved therapies for patients with AD. (APPs with prescribing authority to serve as site co-investigators) • Review all applicable FDA prescribing labels and published Appropriate Use Recommendations for novel FDA-approved therapies for AD • Review the ALZ-NET operations training modules on the ALZ-NET website. • Complete training for research with human subjects (e.g., CITI, GCP, ACRP, Advarra IRB). • Obtain access and complete training specific to the ALZ-NET Electronic Data Capture (EDC) system **Participating Sites 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.

	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. • 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.
Site Payment for participation and data collection	Site start up payment (one time upon activation of site) = $2,500 Per case per time point payments: • Baseline = $300 • Follow Ups = $200 • Image Submission = $50 per image All payments remitted vis electronic funds transfer (EFT) within 30 days of completed time point.

ALZ-NET DATA COLLECTION	SITE START-UP[1]	CASE REGISTRATION[2,6]	BASELINE[3]	FOLLOW-UP[3]
Participating Site Characteristics	x			
Site Investigator (*Prescribing Clinician*) Characteristics	x			
Informed Consent		x		
Eligibility Assessment		x		
Patient Demographics		x		
Concurrent Study Enrollment			x	x
Patient Characteristics			x	o
Medical History			x	
Lifestyle Data			x	o
Vital Signs			x	x
Clinical Features of Co-pathology			x	x
Additional Measures (*Cognitive, Functional, and Behavioral*)			x	x

Clinical Events Form				**x**
Concomitant Medications			**x**	**x**
AD Diagnosis, Characteristics, and Biomarkers			**x**	**x**
Clinical Imaging Submission[4,5]			**x**	**x**
Amyloid PET Assessment*			**x**	**x**
Tau PET Assessment			**x**	**x**
MRI Assessment*			**x**	**x**
AD Treatment and Dosing Log			**x**	**x**
Healthcare Encounters (*Hospitalizations and ER Visits*)			**x**	**x**
Adverse Events (AEs) / ARIA Events			**x**	**x**
End of Participation (Death, Lost to Follow-up, Withdrawal of Consent) – *only if applicable*				**x**

x = Required form o = Optional form

1) Information submitted via the site registration questionnaire and Staff Registration Questionnaire via RedCap portal on ALZ-NET website.

2) Data submitted during patient registration process via the ACR Clinical Trial Web Application

3) Data submitted via one of the ACR approved data transfer mechanisms

4) Data is submitted by site staff via upload of applicable imaging reports into ACR's CONNECT and TRIAD applications

5) Transmission of brain images occur via ACR's CONNECT and TRIAD applications. Patients can 'opt out' of image transmission.

6) Case registration can occur at the same time as the baseline visit but not needed.

** Assessment forms are internal forms to the ACR, completed from data collected via submitted radiology reports.*