Protocol Training for Participating Clinicians and Site Staff

Version 2.0, March 2023

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

- ALZ-NET will collect longitudinal clinical data for enrolled patients being evaluated for or treated with novel FDA-approved AD therapies and track patient long-term health outcomes associated with use of these therapies in real-world settings.
  - 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.
  - Will assess long-term safety of novel FDA-approved AD therapies by capturing adverse events and any events that may be specific to each novel FDA-approved AD therapy over the long-term.
- Will be a resource for evidence gathering, information sharing, and education across clinical and research communities.
- Creation of a national provider-enrolled patient network for novel FDA-approved treatments for Alzheimer's Disease.

ALZ-NET Aims

Aim 1	• 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	• To develop mechanisms to co-enroll participants in affiliated trials
Aim 3	• 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 4	• To merge and compare ALZ-NET data with existing databases to further understand patient outcomes and resource utilization
Aim 5	• To establish and implement infrastructure for sharing of de-identified data, images and biosamples

ALZ-NET: Clinical Care Vs Research

Clinical Care

- Clinician office visits and overall patient care plans
- Diagnostic and evaluation procedures
- Treatment decisions
- Applicable safety imaging and monitoring

Research

- Informed Consent (patients)
- Case report forms (CRF)
  - Clinical care and AE reporting
- Brain image archival
- Collection of participants' health insurance claims
- Contact for future research studies (optional)

Questions ALZ-NET Could Address

Why is ALZ-NET important?

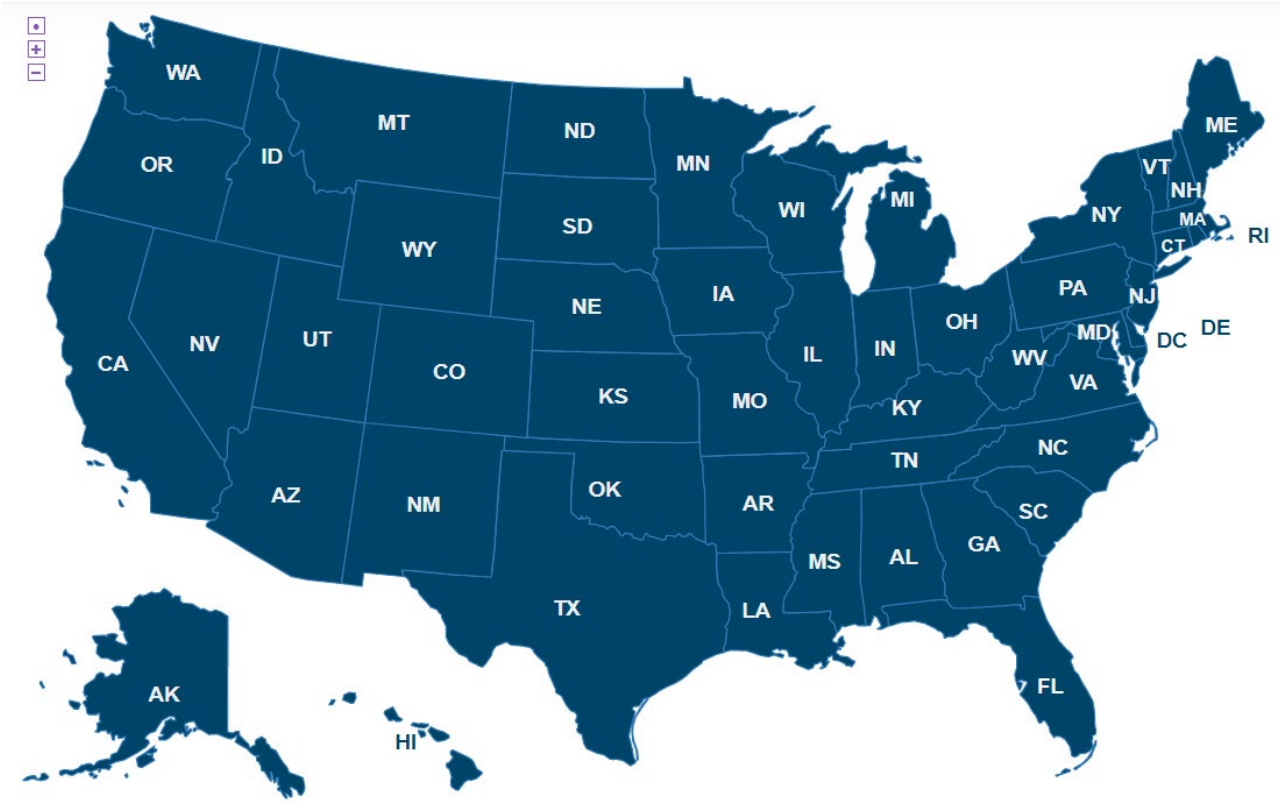
ALZ-NET will be used to build real-world evidence for approved treatments and to support drug discovery programs.

Questions that can be answered with this data set:

- Longitudinal change across treatment duration
- Identifying responders and non-responders, predictors of response and non-response
- Compare aggregated data on outcomes across MOA and classes of therapeutics

ALZ-NET Site Participation

- Sites that meet the minimum criteria and have submitted the Site Feasibility and Registration Questionnaire are invited to participate.
- ALZ-NET is constantly growing the network of sites and providers; spanning all geographic areas and applicable care settings.
- To look at currently active sites, navigate to the Site Finder



Participating Site Requirements

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 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
- Access to standard cognitive, behavioral, and functional assessments used in dementia care

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 Staff Registration Form.

Collected data elements will include:

- Investigator's name and contact information (solely for ALZ-NET operational purposes)
- National Provider Identification Number (NPI)
- Type of provider
- Board Certifications and Sub-specialties
- Experience in dementia care
- Experience with novel FDA-approved AD therapies

Patient Inclusion Criteria

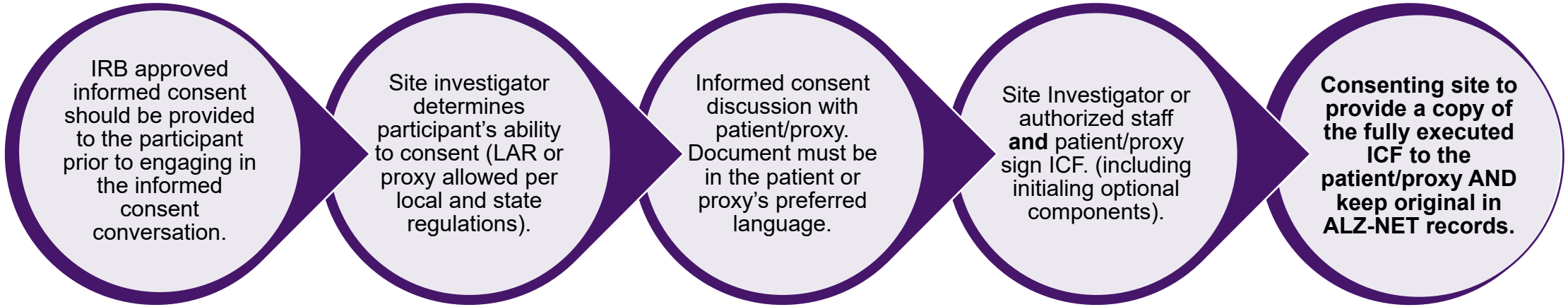
- Patient or patient's legally authorized representative (LAR) or proxy (e.g., spouse or legal guardian) has the ability to understand the purpose and risks of ALZ-NET and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local patient privacy regulations.
- Patient is at least 18 years or older at time of informed consent
- 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
- 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.
- Patient's treating clinician has made the decision to treat the patient with novel FDA-approved therapy for AD independent of the purpose of ALZ-NET and has already or will be initiating treatment

Informed Consent Process Overview

Best Practice:
Face to face, in-person informed consent

Electronic and remote consenting procedures are permitted

If a Legally Authorized Representative (LAR) is used, LAR's signature and date are required on the ICF AND LAR's initials must be documented on optional consent components.

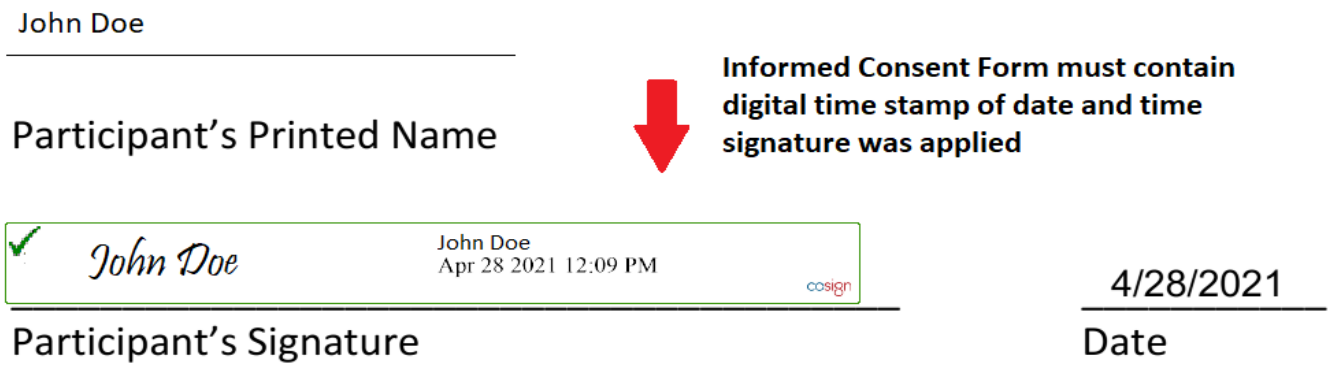


Informed Consent Process

Obtaining Electronic Signatures

Advarra IRB Guidance on Remote Electronic Signatures

- The site staff must have a discussion with the patient (and document this process) and not simply send the patient the form.
- Electronic signatures must meet 21 CFR Part 11 Compliance.
- The electronic signature system (including, but not limited to, DocuSign, Adobe, and Cosign) must have date/time stamp functionality and document:
  - The printed name of the signer
  - The date and time that the signature was applied.
  - The meaning of the signature. This is fulfilled by the signature line identifying who is signing (i.e. patient, LAR, witness, etc.)



Informed Consent Process

Obtaining Electronic Signatures

- Sites may fax/email the consent form to the patient and have them fax/email it back.
- When a copy of the fully executed ICF is returned to the study team, informed consent may be obtained by telephone/videocall. When obtaining consent by telephone/videocall, researchers must:
  - Document how the ICF was transmitted to the participant (e.g., email, fax, mail, etc.).
  - Document how the participant's signature was obtained. For example:
    - Electronic signature.
    - Scanned and emailed, faxed, or mailed back to the study team.
    - Photograph of signature/signature page sent back to the study team.

Additional resources found on ALZ-NET website

Expectations of ALZ-NET

Main Consent Elements

- Consent to allow the clinical site to provide ALZ-NET with clinical and brain imaging data related to dementia care for the duration of participation
- Provide name, address, social security number, health insurance identification number, date of birth, and contact information.
- Continue to visit treating clinician and receive care as would normally be provided, outside of participation in ALZ-NET.
- Allow ALZ-NET to collect and analyze health insurance claims data for five (5) years prior to enrollment for the duration of participation in ALZ-NET.
- Allow ALZ-NET to share de-identified data with external researchers for use in future dementia related research

Future Research Opportunities

- Participants must **opt in** on the ICF in order to be contacted about other research opportunities.
- Participants who opt in will be contacted by the Alzheimer's Association TrialMatch™ staff
- TrialMatch™ staff will confirm participant's interest in specific affiliated studies for which they may qualify and explain who may be contacting them for each specific affiliated study.
- Participation in any affiliated study is independent from participation in ALZ-NET.

ALZ-NET Data Collection Timepoints

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). Patient visits should occur per the treating clinician's standard timelines.

Sites should refer to the detailed table of data elements and the case report form packet to know what data should be captured in participants' medical records.

Participating sites are required to provide follow-up clinical visit data in the EDC at the following timepoints after baseline:

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

ALZ-NET Additional Assessments

Required Assessments
Mini-Mental State Evaluation (MMSE)
Montreal Cognitive Assessment (MoCa)
Functional Activities Questionnaire (FAQ)

Optional Assessments
AD8 Dementia Screening
Neuropsychiatric Inventory (NPI)

- Medidata Rave, the EDC for ALZ-NET, has an option to record that an assessment has not been completed when registering a patient.
  - For baseline visits, please put the most recent assessment data that is part of the patient's medical record.

- ALZ-NET sites are authorized to use the Functional Activities Questionnaire (FAQ) and AD8 that are found on www.alz.org

ALZ-NET does not currently provide forms for the cognitive and additional assessments. ALZ-NET is seeking a national license for MoCA/MMSE and NPI-Q, that would make the assessments available to sites that are participating.

Applications Used for Data Transfer

- **RedCap**
  - Site Registration and Feasibility Form
  - Staff Registration Form
- **CTMS (*Clinical Trial Management System*)**
  - Case Registration – consent, eligibility, and demographics.
  - Also referred to as Clinical Trial Web Application
- **DART (*Data Analysis and Research Toolkit*)**
  - Patient Identifiable Information
- **MediData RAVE**
  - Electronic Data Capture (EDC) – all timepoints
- **ACR TRIAD**
  - Transfer of brain images and associated radiology reports using TRIAD application

ALZ-NET Schedule Overview

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

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.*

Brain Imaging in ALZ-NET

- All diagnostic and safety monitoring imaging procedures that ALZ-NET participants undergo should be conducted per local practice, applicable procedure standards and appropriate use guidelines.
- Participating sites are expected to obtain brain images and accompanying reports from the imaging facility that provides the imaging services
  - Sites then provide images and reports to ALZ-NET via ACR TRIAD
  - Brain images to be transferred include amyloid PET, Tau PET, and MRI

ALZ-NET provides resources and recommendations regarding training, acquisition, scanners, sequencing, and reporting guidelines and templates on the ALZ-NET website.

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 unless informed consent is withdrawn.
- 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 change or discontinuation occurs 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.

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
- In the event that a patient is transferring care to a new ALZ-NET site, the participant must be re-registered by that site

Participation End Points

- 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 meet on of the below endpoints, ALZ-NET will continue to collect data.
    - **Withdraw 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.
    - **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.
    - **Patient death**
    - **Termination of the current provider site's participation in ALZ-NET**
    - **Closure of ALZ-NET**

Adverse Events Reporting

An Adverse Event (AE) form must be submitted at all follow up time points for registered patients that had a reportable event. Reportable events are defined 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 grade 3 or higher, per CTCAE grading scale
- 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)

Sites must 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.

Health Insurance Claims Data

- ALZ-NET will collect health insurance claims from enrolled participants
  - The American College of Radiology CRI Data Management Center and Brown University Statistical Center will coordinate claims data collection and analysis
- Proper informed consent and authorization to collect healthcare claims will be collected for all ALZ-NET participants via the IRB-approved ICF.
  - Participant's informed consent authorizes collection of their health insurance claims data for a time period of five (5) years prior to their enrollment in ALZ-NET and ahead, unless consent is 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

Co-Enrollment in Affiliated Studies

- ALZ-NET will partner and collaborate with affiliated studies to facilitate co-enrollment for patients receiving novel FDA approved AD therapies.
- Participants will be required to provide separate informed consent authorization for any affiliated studies to which they co-enroll.
- A separate registration process will also occur
- Any overlapping data elements being collected by ALZ-NET and an affiliated study will only require data entry one time by participating sites.
- All participating sites and patients should refer to applicable affiliated study protocols and informed consent forms for additional information.

Protocol Violation

- **Any 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 violation should result in an **immediate email communication** to ALZNET-Regulatory@acr.org.
- **Protocol violation documentation will require the following:**
  - Case # and Advarra Protocol #
  - Description of the violation
  - IRB acknowledgement, note that IRB will review at the next quarterly review period, or IRB feels this deviation does not warrant review.
  - Corrective action plan (CAPA)
  - Ensure that all information provided by Site is Redacted.
- **Protocol violations may include, but are not limited to:**
  - Changing of protocol/consent without IRB approval
  - Use of non-current ICF to consent patients
  - Failure to consent patient who is enrolled.
  - Breach of confidentiality

Central IRB Overview

- **Referring physician sites must use Advarra IRB as the IRB of record.**
- **Local IRBs are <u>not</u> permitted** to serve as the IRB of record for ALZ-NET.
- **IRB approval of each site and their ICF is required prior to full activation by the ACR.**
- Each site is responsible for notifying the ACR **and** the Central IRB (Advarra) if any revisions are made to their ICF during their participation in ALZ-NET.
- Advarra IRB protocol number for ALZ-NET: **Pro00064645**

ALZ-NET Operations Team

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