Protocol Training

For Participating Clinicians and Site Staff

Version 3.0, December 2023

ALZ-NET Operations Team Office Hours

Every Tuesday from 12pm-2pm EST
Every Wednesday from 2pm-4pm EST

Click to
Join ALZ-NET Office Hours

American College of Radiology™
Center for Research and Innovation

Connect with the ALZ-NET Operations Team at the American College of Radiology (ACR)

Topics include, but are not limited to:

- *Study start-up assistance*
- *Protocol review**
- *Contract support*
- *IT support*
- *Database support*
- *Regulatory guidance*
- *General operations*
- *Billing and reimbursement guidance*

To **schedule a formal site protocol training, email alz-net@acr.org.*

ALZHEIMER'S NETWORK

ALZ-NET Overview

Background
Protocol Aims
Clinical Care vs Research
Coverage with Evidence Development (CED)

What is the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET)?

- A **national provider-enrolled patient network for patients being treated with novel U.S. Food and Drug Administration (FDA)-approved therapies* for Alzheimer's disease (AD).**

  **Refers to drugs approved as treatments for AD by the U.S. FDA since 2021*

- ALZ-NET will:
  - **Collect longitudinal clinical data from patients.**
  - **Track long-term health outcomes** associated with the use of these therapies in real-world settings.
  - **Assess therapy-specific safety data in the long term** through the capture of therapy-related events and adverse events.
  - **Serve as a resource for evidence gathering, information sharing, and education** across clinical and research communities.

Why is ALZ-NET Important?

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

With ALZ-NET data, we may be able to:

- Study longitudinal change across treatment duration.
- Identify responders and non-responders and predictors of response and non-response.
- Compare aggregated data on outcomes across mechanism of action and classes of therapeutics.

Protocol Aims

Aim 1	Establish the necessary network infrastructure for **database development**, **image repository** and **biorepository.**
Aim 2	To develop mechanisms to **co-enroll participants** in affiliated trials.
Aim 3	Collect data to **evaluate long term safety, clinical use and outcomes.**
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.**

ALZ-NET: Clinical Care vs Research

Sites enrolling patients into ALZ-NET will follow **standard clinical care** procedures **AND** engage in **research-specific** procedures.

Clinical Care

- Clinician office visits.
- Management of ongoing patient care plans, including:
  - Diagnostic and evaluation procedures.
  - Treatment decisions.
  - Applicable safety imaging and monitoring.

Research

- Obtain patient informed consent.
- Data submission, including:
  - Case report forms (CRF).
  - Clinical care data and adverse event (AE) reporting.
  - Brain image archival.
  - Patient contact for future research studies *(patient may opt-in).*
- ALZ-NET Team will collect participants' health insurance claims.

ALZ-NET Affiliated Coverage with Evidence Development (CED) Study

What is CED?

- A program whereby Medicare covers items and services on the condition that they are provided in the context of approved clinical studies or with the collection of additional clinical data.

Is ALZ-NET a CED Study?

- Yes. ALZ-NET was approved as a CED study by the Centers for Medicare and Medicaid Services (CMS).

What does this mean for my patients?

- Patient registration into ALZ-NET is a pathway to Medicare coverage for anti-amyloid Alzheimer's therapies* that have received traditional FDA approval.

Additional CED Details	
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*
Sponsor	*The American College of Radiology*
ClinicalTrials.gov Number	NCT06170268
CMS Approval Date	January 29, 2024
***Current list of CED applicable therapies**	LEQEMBI® (lecanemab)

Getting Started

Site Activation
Institutional Review Board
Data Applications

Review Participating Site Requirements

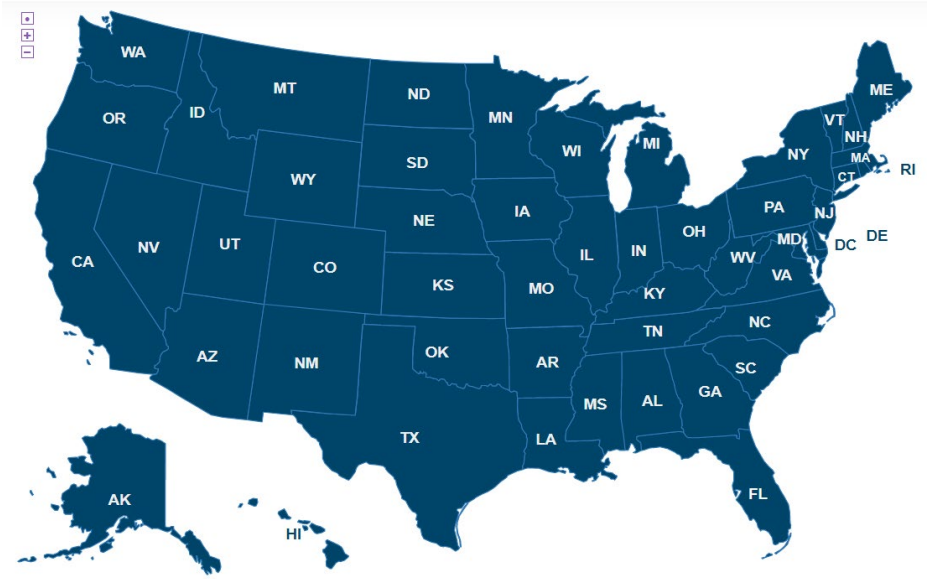
Each participating site **must** demonstrate the **use of a multi-disciplinary dementia care team** and **optimal medical management.**

Additionally, sites must:

- ✓ Have clinical expertise AND an infrastructure to provide novel FDA-approved AD therapies consistent with the safety monitoring outlined in applicable FDA approved labels.
- ✓ Have access to:
  - Accredited and appropriate radiological services for diagnostic and safety brain imaging
  - Infusion services
  - Emergency services
  - Standard cognitive, behavioral, and functional assessments used in dementia care

Complete the Site Feasibility and Registration Questionnaire

- All interested sites **must** complete a **site feasibility and registration questionnaire** to receive an invitation from ALZ-NET to participate.
- Participating sites will be recruited and invited to participate **on a rolling basis.**
- Contact alz-net@acr.org to check your application status.



Sites will be identified via the IDEAS Study network, affiliations with the Alzheimer's Association and partnering organizations, applicable national societies, as well as national media outreach.

Complete Site Start-up Activities

Every Tuesday from 12pm-2pm EST
Every Wednesday from 2pm-4pm EST

Join ALZ-NET Office Hours

Complete the Site Activation Checklist *after* your site receives an official welcome invitation email from the ALZ-NET Operations Team.

Click to view the full **Site Activation Checklist**

Note: All steps can occur simultaneously to expedite the start-up process.

- ✓ Fully execute the ALZ-NET Research Agreement*
- ✓ Obtain Advarra Institutional Review Board (IRB) Approval (Slide 15)
- ✓ Complete Human Subject Protections Training
- ✓ Complete Staff Registration Form for each staff member (Slide 14)
- ✓ Register for access to data applications (Slide 16)
  - ✓ Case Registration (RMS)
  - ✓ Electronic Data Capture (Medidata Rave)
  - ✓ Image submission, if applicable (TRIAD)
- ✓ Complete Protocol Training Acknowledgement Form, as applicable:
  - For Principal Investigators
  - For Site Support Staff
- ✓ Send Site EFT Vendor Information and W-9 to ALZ-NET Operations Team at alz-net@acr.org.

**included in welcome email*

Complete the Staff Registration Form

Prior to completing the Staff Registration Form, please ensure the following information is available to you:

- Site ID number (in welcome packet)
- **For each staff member AND site investigator:**
  - First and Last Name
  - Email address
  - Human Subjects Protections Training
  - Data application access needs (Slide 16)
- **For each site investigator:**
  - National Provider Identification Number (NPI)
  - Type of provider
  - Board certifications, subspecialties and fellowship training
  - Proportion of time devoted to dementia care
  - Years of experience in dementia care
  - Experience with novel FDA therapies
  - Patient Enrollment Chain and Ownership System (PECOS) status

Central IRB Overview

CIRBI

Quick Access to the CIRBI Platform

Referring physician sites **must use Advarra IRB as the IRB of record.** Local IRBs **cannot** be the ALZ-NET IRB of record.

- Advarra IRB protocol number for ALZ-NET: **Pro00064645**
- **Prior to full site activation**, a site **must:**
  - Obtain site-level IRB approval
  - Receive approval of site-specific informed consent form (ICF)
- **During the study,** a site **must:**
  - Notifying ACR AND Advarra IRB if any revisions are made to their ICF.

ADVARRA

Read More on the IRB Approval and Informed Consent Process

Data Applications

Tip: ALZ-NET staff submitting data should ***save web browser bookmarks for the following ACR applications:***

RMS
Research Management System

View Training Module

- Consent verification
- Eligibility verification
- Demographic data
- Patient identifiable information (PII)

medidata
Medidata RAVE

View Training Module

Electronic Data Capture (EDC) for all study timepoints (e.g., baseline visit, 6-month visit, etc.).

TRIAD
ACR IMAGE AND INFORMATION EXCHANGE

View Instructions

Transfer of brain images and associated radiology reports.

ALZHEIMER'S NETWORK

Eligibility and Screening

Patient Eligibility
Informed Consent Process
Expectations for Study Participants

ALZ-NET Patient Inclusion Criteria

Prior to participant registration, the site must confirm ALL the following inclusion criteria are TRUE:

1. The patient or patient's legally authorized representative (LAR) or proxy has the ability to understand the purpose and risks of ALZ-NET, including providing signed and dated informed consent and authorization to use protected health information (PHI).
2. Patient is at least 18 years or older at time of informed consent.
3. Patient has a diagnosis of Mild Cognitive Impairment (MCI) or dementia with clinical suspicion of 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 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.

CED Cohort Inclusion Criteria

Effective January 29, 2024, enrollment into ALZ-NET permits coverage of traditionally approved* monoclonal antibodies treatments directed at AD **for Medicare beneficiaries.**

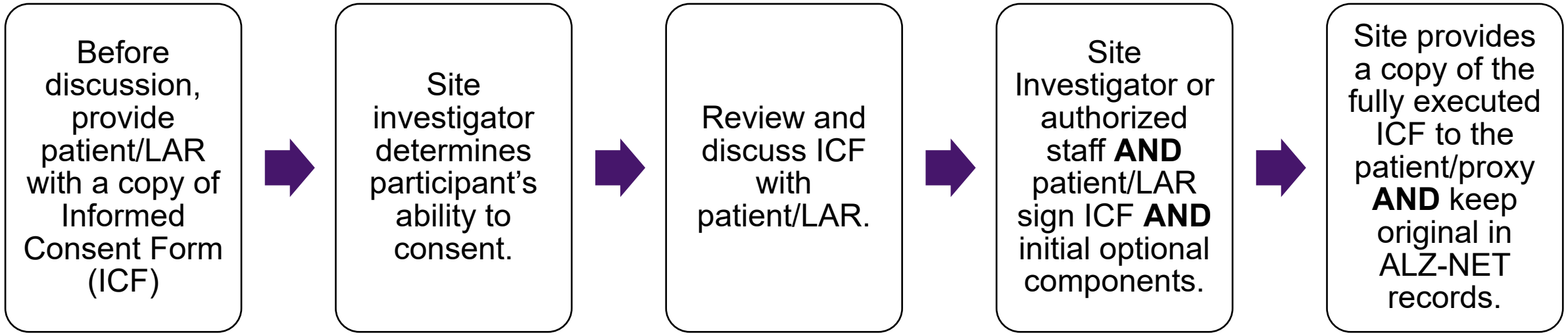
ALZ-NET Billing Guidance for CED

Therapies that are covered under this CED approval include: LEQEMBI™ (Lecanemab)

Patients **may be eligible** to be a part of the CED Cohort **if they meet the following inclusion criteria**:

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 *is allowed.*
3. **Being treated with a beta-amyloid targeting monoclonal antibody** that has received traditional FDA approval for the treatment of AD.

Informed Consent Process Overview



ICF **must** be in the patient's or Legally Authorized Representative (LAR)'s **preferred language.**

LAR or proxy allowed per local and state regulations.

Face to face, in-person is best practice. Remote/electronic* consent permitted

LAR must sign and date where required **AND** provide **LAR's initials** on optional components.

*See Slide 21

Obtaining Electronic Signatures and Remote Consent

If planning complete any of the following consent activities, **confirm you are complying with Advarra IRB's regulations:**

Click to Review Guidance for Electronic and Remote Informed Consent

Obtaining Electronic Signatures:

Determine if your site is using any electronic or digital signature that falls under the eConsenting Category.

→

Submit a modification to Advarra IRB for Electronic Signature Use *prior* to obtaining consent.

→

Follow Advarra Guidance for Obtaining Electronic Signatures.

Handwritten Signatures in a Digital Format:

- The signer's identity needs to be verified.
- Signatures obtained in-person; not over email/video call.
- The signature must be done in such a way that cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

Obtaining Signatures Remotely:

1. Site fax/email ICF to patient.
2. Patient completes ICF sections and fax/emails it to site.
3. Site complete ICF discussion by phone/videocall.
4. Site must document:
   - How ICF was transmitted to the participant (e.g., email, fax, mail, etc.).
   - How the participant's signature was obtained (e.g. Electronic signature, scanned and emailed, faxed, or mailed; photograph of signature/signature page sent to site).

Expectations for Study Participants

ALL participants who consent to participate in ALZ-NET are consenting to:

Allow the **clinical site to provide ALZ-NET:**

- **Clinical and brain imaging data related to dementia care** for the duration of participation.
- **Personal Identifiable Information** including 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 researchers** to:

- **Collect and analyze health insurance claims data** for five (5) years prior to enrollment AND for the duration of participation in ALZ-NET.
- **Share de-identified data with external researchers** for use in future dementia related research

SOME participants may **OPT IN** on the ICF to be contacted about other research opportunities:

Alzheimer's Association TrialMatch™ staff will contact a patient who consents to future research to 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. *Note: Participation in any affiliated study is independent from participation in ALZ-NET.*

Data Collection

Data Submission
Additional Measures
Imaging Submission
Co-enrollment
Reportable Events
Claims Data Collection

Data Collection Schedule

Timepoint	Data Collected	Data Application
Study Start-up	• Participating Site Characteristics • Site Investigator (Prescribing Clinician) Characteristics	• Site Feasibility and Registration Form • Staff Registration Form
Case Registration	• Informed Consent • Eligiblity Assessment • Patient Demographics	RMS Research Management System
Baseline and Follow-up *designates optional at follow-up.	• Concurrent Study Enrollment • Patient Characteristics* • Medical History • Lifestyle Data* • Vital Signs • Clinical Features of Co-pathology • Additional Measures (cognitive, functional, behavioral) • Concomitant Medications • AD Diagnosis, Characteristics and Biomarkers • Brain Imaging Clinical Data • AD Treatment and Dosing Log • MRI Assessment • Health Encounters (Hospitalizations and ER Visits) • Adverse Events • End of Participation (Death, Lost to Follow-up, Consent Withdrawn) if applicable	medidata Medidata RAVE
	• Brain Image(s) Transmission	TRIAD ACR IMAGE AND INFORMATION EXCHANGE

Data Entry Requirements

The **participating site** should complete the following tasks **for each patient who consents** to participate in ALZ-NET:

Standard Clinical Care

- Patient's clinician **prescribes treatments at clinician's discretion.**
- Patient's treating clinician **monitors patient according to patient needs and local standard of care (SoC).**
- Clinician office **schedules patient visits** per the treating clinician's standard timelines.

*Note: Refer to **detailed table of data elements (Slide 24)** and the case report form packet indicate which data should be captured in participants' medical records.*

ALZ-NET Data Entry

- **Submit participant registration data in RMS** at:
  - Baseline
- **Submit clinical visit data in Medidata Rave** at:
  - Baseline
  - 6 months
  - 12 months
  - 18 months
  - 24 months
  - Annually thereafter until participation endpoint is met
- **Submits images to TRIAD**, when available.

Additional Measures

Required data elements **must be collected by authorized clinical staff** during standard of care clinical visit AND **documented in the patient's medical record.**

Baseline: Report on the most recent assessments performed. *(Note: select "not completed" if not available at time of registration)*

Follow-Up: Report on all assessments performed during the reporting period.

Required Assessments	**Optional** Assessments
• Mini-Mental State Evaluation (MMSE)* • Montreal Cognitive Assessment (MoCa)* • Functional Activities Questionnaire (FAQ)	• AD8 Dementia Screening • Neuropsychiatric Inventory (NPI)*

ALZ-NET sites are authorized to use the **Functional Activities Questionnaire (FAQ)** and **AD8** at 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.*

Brain Imaging in ALZ-NET

All diagnostic and safety monitoring imaging procedures 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.
  - Brain images to be transferred include amyloid PET, Tau PET, FDG PET, and MRI
- Provide images and reports to ALZ-NET via ACR TRIAD

View ALZ-NET resources and recommendations for:

- Training
- Acquisition
- Scanners
- Sequencing
- Reporting guidelines and templates

Co-Enrollment in Affiliated Studies

Patients registered in ALZ-NET may **co-enroll** in an ALZ-NET affiliated study.

The following must occur for co-enrollment (when applicable):

- Separate patient informed consent authorization for each affiliated study.
- Separate patient registration process.
- One time data entry for any overlapping data collected in the ALZ-NET protocol.
- Sites and patients should refer to applicable affiliated study protocols and informed consent forms for additional information.

Discontinuation or Change of Treatment

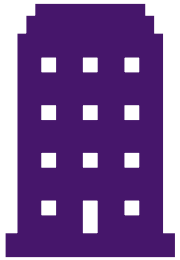
Participants who switch treatments, or discontinue treatment altogether, will continue participating in ALZ-NET **unless informed consent is withdrawn.**

- Treating clinician records the **primary reason for drug change or discontinuation**, including any Adverse Events (AE) 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 if 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 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.

ALZ-NET participants will continue to receive care and data collection will continue, **unless one of the following conditions are met:**

- **Patient withdraws consent.** Patients may withdraw consent to participate in ALZ-NET at any time with no effect on their medical care or access to treatment.
- **Patient is 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

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.

An **Adverse Event (AE) Form** must be submitted at all follow-up time points for registered patients who experienced a reportable event. Submission is required 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 using attribution categories of possible, probable, and definite.
- All serious adverse events (SAEs).

Protocol Violations

CIRBI

Quick Access to the CIRBI Platform

If a protocol deviation is identified, **the site must**:

- **Immediately email** ALZNET-Regulatory@acr.org.
- **Report the violation** to the IRB of record **within 2 weeks (10 business days)** from the time the violation was identified.
  - Redact all PHI from submission
  - Include:
    - Case ID #
    - Advarra Protocol #
    - Description of the violation
    - Corrective Action Plan (CAPA)
- **Save IRB acknowledgement*** and additional documentation with patient file. (**Note: If review is required, the IRB will review at the next quarterly review period).*

Examples:

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

For additional guidance, email ALZNET-Regulatory@acr.org.

Health Insurance Claims Data

The ALZ-NET ICF authorizes:

- Collection and analysis of patient health insurance claims data for a period of five (5) years prior to their enrollment in ALZ-NET and throughout their participation, **unless consent is withdrawn.**
  - Collection and analysis will be completed by the American College of Radiology (ACR) Center for Research and Innovation (CRI) Data Management Center and Brown University Statistical Center.
  - Claims data will be collected directly from applicable insurance companies.

Important Reminders:

- *Claims data collection from insurance companies is 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.*

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