The 2024 Zenith Fellows Award Program (ZENITH)

BACKGROUND
The Alzheimer’s Association was founded in 1980 by a small group of family members caring for loved ones with Alzheimer's disease. Two years after its founding, the fledgling organization funded its first research grant, awarding a total of about $80,000 to a handful of investigators. Since then, the Association has grown into the largest nonprofit funder of Alzheimer’s research.

Today, the Alzheimer's Association leads the way to end Alzheimer's and all other dementia — by accelerating global research, driving risk reduction and early detection, and maximizing quality care and support. In pursuit of its vision of a world without Alzheimer’s and all other dementia, the Alzheimer’s Association has active and committed funding to more than 1,000 best-of-field projects, totaling over $360 million in 53 countries. Our funding has contributed to nearly every critical breakthrough in Alzheimer's research.

The Association supplements its own funding efforts with public policy initiatives directed toward increasing support for Alzheimer’s and all dementia research at the federal level. The Association's International Research Grant Program has served historically as an incubator for novel ideas, complementing the programs of federal agencies around the world, including the National Institute on Aging and other institutes of the National Institutes of Health. As our funding initiative has grown and matured, grant categories have expanded to support researchers at every stage in their careers. Funded projects now explore the broadest possible spectrum of studies to understand, prevent and treat Alzheimer’s and all dementia, and to ameliorate the effects of dementia on patients, families, and caregivers through social and behavioral strategies, clinical studies, and adaptive technologies.

PROGRAM OBJECTIVE
The Zenith Fellows Award was initiated in 1991 as a vehicle for donors with a substantial personal commitment to propel research in Alzheimer’s and all other dementia research. The awards are made possible by the generosity of individuals and organizations (Zenith Society) who have each committed $1 million to the Alzheimer’s Association in support of the program.

The objective of the 2024 Zenith Fellows Awards competition is to provide funding support for investigators who have:

- Contributed significantly to dementia science including Alzheimer’s and all other dementia research
- Contributed significantly to neuroscience breakthroughs that have informed our broader understanding of Alzheimer’s and other dementias
- Are likely to make substantial contributions in the future.

The proposed research should address fundamental problems related to early detection, etiology, pathogenesis, treatment, or prevention of Alzheimer’s and all other dementia. We seek proposals at the cutting edge of basic science or biomedicine that may challenge prevailing orthodoxy or not conform to traditional funding mechanisms, but which promise a sustained and positive impact on the future of dementia research.
AREAS OF FOCUS
The Alzheimer’s Association supports a number of high priority areas that span the entire spectrum of science and have other programs throughout a given year, however, the Zenith Fellows program is unique in focusing specifically on biological studies and clinical investigations (excluding clinical trials). Innovative and novel ideas to address research challenges are the core of the Alzheimer’s Association's scientific program. The Alzheimer’s Association is committed to minimizing health disparities and increasing representation of all populations within research and clinical trials.

Basic biology: these are bench science projects involving in vitro or animal work pertaining to the causes of dementia; early and accurate detection and diagnosis; animal models; treatments; and prevention. Basic biology may also include computation studies, such as data mining for genes linked to risk, or other bioinformatic studies. Please note that in vitro work involving human samples falls into this category.

Clinical investigations (this does not include clinical trials): projects in which the majority of data is derived directly from studies of human participants. Examples include studies that aim to evaluate potential therapeutic approaches; promising biomarkers; imaging technology; and possible risk factors including genetics, lifestyle, cardiovascular issues, diabetes, and metabolic factors. In vitro projects conducted with human samples should be categorized as basic biology rather than clinical investigations. Note that this definition of clinical investigation does not extend to clinical trials which will not be considered for funding under the Zenith program.

Although vast advances have been made in Alzheimer’s and ADRD research, the field still faces a great number of serious impediments in translating basic science discoveries into effective treatments and evidence-based clinical practices for dementia. Some of the many challenges that remain for investigators to address include:

Cause(s) of Alzheimer’s and ADRD
- How do specific neurons in vulnerable brain structures become dysfunctional?
- What causes selective neuronal death in some brain regions but not others?
- What factors initiate these processes and what are key steps leading to cell death?
- How do genetics interact with other factors to influence these processes?
- What factors tip the balance between effective removal or pathological accumulation of toxins in the brain?
- How do risk factors interact to promote disease, and how do they underlie specific neurologic/neuropathologic changes in the brain?

The primary neuropathological events in Alzheimer’s and other dementia involve aberrant formation of pathologic protein species. Advances in molecular biology provided the tools to unravel mechanisms of synthesis, trafficking, and accumulation of these proteins in the brain. Research in this area has produced promising leads about the role of these proteins in neural function, dysfunction, and cell death, while also suggesting strategies to correct this molecular damage. Although these insights have generated many hypotheses, the precise etiology of Alzheimer's disease and other dementias is still not known. Critical questions remain.

The precise relationships between clinical symptomatology and neuropathology are not well defined. There is a critical need to understand not only the causal links between neurobiology and clinical progression, but also the mechanisms for heterogeneity in clinical presentation. These mechanisms may vary widely and may influence both differential diagnosis and treatment response.
Early and Accurate Detection and Diagnosis

- What are the most sensitive, specific and cost-effective diagnostic procedures?
- What are the most sensitive, specific and cost-effective procedures for assessing change through the course of the disease?

Several converging lines of evidence suggest that the neurodegenerative processes associated with dementia begin several years before the first clinical features can be detected with current instruments. Although clinical information can be gleaned from longitudinal studies, these data are usually obtained in the middle to later stages of the disease when initial cognitive and behavioral signs have already manifest. As a result, there is little information on disease presentation during its earliest preclinical stages. These gaps result from a lack of non-invasive tools for observation and early detection of the disease. Finding sensitive and specific markers will become even more important as pressure increases to develop very early treatments, especially if these early interventions have the potential for harmful side effects and must be targeted appropriately. Thus, there is an urgent need to find accurate, accessible biological markers of disease that are applicable to all populations. These include imaging techniques and more culturally sensitive cognitive and behavioral assessment instruments.

Well-tested biological markers for Alzheimer’s and other dementias are not the only critical need—investigators are also encouraged to explore the observational and subjective perspective that family members, care providers, and people with the illness can provide about the very earliest events. The observations of family members, nurses, social workers, and other care providers have already provided important insights about early cognitive and behavioral events.

Risk Factors

- What genetic or acquired characteristics increase the risk of Alzheimer’s and other dementias?
  - Conversely, what factors offer protection or delay onset?
- How do the risk factors vary among representative populations?
- Which risk factors are modifiable, and when in life does intervention have the greatest impact?

Growing evidence suggests that most cases of Alzheimer’s and other dementias involve a combination of genetic and environmental risk factors, with some populations being disproportionately affected. Identifying and validating these risk factors remains a critical challenge. For instance, there is a potential link between cerebrovascular disease and Alzheimer’s, but we do not yet know if systemic vascular or metabolic factors modify risk for Alzheimer’s and other dementias.

**FUNDING AND AWARD PERIOD**

We anticipate funding up to three Zenith Fellows Awards. Each award is limited to $450,000 total funding (direct and indirect costs) over a period of up to three years. Requests in any given year may not exceed $250,000 (direct and indirect costs). Additional details on allowable costs are outlined in the budget section below.
**KEY DATES**

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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<tr>
<td>Letter of Intent Launch</td>
<td>October 16, 2023</td>
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<tr>
<td>Letter of Intent Deadline*</td>
<td>November 14, 2023, 5:00 PM EST</td>
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<tr>
<td>Letter of Intent Notifications</td>
<td>Week of January 15, 2024</td>
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<tr>
<td>Application Deadline*</td>
<td>March 15, 2024, 5:00 PM EST</td>
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<td>Application Review</td>
<td>March - July 2024</td>
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<td>Award Notifications</td>
<td>by August 30, 2024</td>
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*The Letter of Intent and application must be received by 5:00 PM EASTERN TIME on their respective deadlines. They will not be accepted after these dates -- no exceptions will be made. Hard copies or emails will not be accepted.

**ELIGIBILITY**

- Only established independent investigators are eligible as evidenced by:
  - Academic level: Associate Professor or above;
    - Applicant must be an Associate Professor or above at the time of application
  - Major, peer-reviewed, external multi-year grant support on which the applicant serves as principal investigator (PI);
  - Independent laboratory operation;
  - Quality and independence of publication record
- Only applicants who have already contributed significantly to the field of Alzheimer’s and other dementia research and/or have the clear likelihood of making significant contributions will be seriously considered.
- The Alzheimer’s Association recognizes the need to increase the number of scientists from underrepresented groups in the research enterprise. Researchers from these groups are encouraged to apply.

In general, scientists and clinicians from public, private, domestic and foreign research laboratories, medical centers, hospitals and universities are eligible to apply. State and federal government-directed laboratories (both U.S. and abroad) and for-profit organizations are prohibited from serving as the applicant institution, however, state and federal government scientists can participate as collaborating scientists with research teams from other eligible applicant institutions.
For US entities, the Letter of Intent (LOI) must include proof of your organization’s not-for-profit status and a W9 signed and dated by the signing official. Non-US entities must provide a W8 signed and dated by the signing official. LOIs without this documentation will not be accepted. An IRS Letter of Determination is no longer accepted. For non-academic non-profit organizations, additional documentation may be required to confirm your organization has segregation of duties between transaction execution and transaction utilization.

The Alzheimer’s Association reserves the right to request additional documentation to verify an applicant’s status should any of the eligibility requirements be unconfirmed.

**INELIGIBILITY**

- **Previous recipients of Zenith Fellows Awards are ineligible**
- **Overlapping funding** of more than one Alzheimer's Association grant **is not allowed**. Investigators who currently have an active Association grant may apply for another award in the last year of their grant if that last year concludes before the start of the new funding year on July 1. There are some exceptions; please contact grantsapp@alz.org if you have questions regarding your eligibility.
- **Investigators delinquent in reporting**: The Alzheimer's Association will not accept new grant applications from currently funded investigators who are delinquent in submitting required reports or other deliverables on active grants. Investigators that have previous Alzheimer’s Association awards closed as ‘Incomplete’ are not eligible to apply. **This policy will be strictly enforced with no exceptions.**
- **Current members of the Association's Medical and Scientific Advisory Group (MSAG), the International Research Grant Program (IRGP) Council, and current employees of the Alzheimer's Association** are ineligible to (a) compete for any research grant or (b) be included as a co-investigator or (c) receive any financial benefit from an application. These individuals may be listed as key personnel or collaborators on an application and will be recused from participating in their peer-review.

**BUDGET**

A “budget summary” for the proposed research project is required and must be submitted with the application and within the allowable two-page limit. **Your budget must not exceed $250,000 in any given year nor exceed $450,000 total across all years, including indirect costs.** The minimum award duration is 2 years – awards cannot be for only one year. It is required that most of the funds awarded under this program be used for direct research support. **No more than 10% of the total award may be used for indirect costs; this is inclusive of indirect costs for the implementing institution as well as any subcontracts.**

**Allowable costs under this award include:**

- Purchase and care of laboratory animals
- Pieces of laboratory equipment and laboratory supplies up to USD$10,000. **Purchases over $10,000 require prior approval, even if included in the proposed budget.**
- Computer software if used strictly for data collection
- Salary for the principal investigator, scientific (including postdoctoral fellows) and technical staff (including laboratory technicians, and modest administrative support)
- Research supplies needed for the proposed studies
- Support for travel to scientific and professional meetings, not to exceed $1,000 in any given year
- Open access publication fees for journal articles related to the funded research project
- Membership in ISTAART, the professional society of the Alzheimer’s Association
● Participant travel for studies involving human volunteers is an allowable cost. Travel for study participants should not be included in travel expenses, but should be listed as an "other expense" and itemized in the budget.

Not allowable as Direct Costs under this award include:
● Computer hardware or standard software (e.g. Microsoft Office, monitors, computer parts)
● Major pieces of laboratory equipment such as freezers, ultracentrifuges, RT-PCR machines, microscopy/imaging equipment (regardless of whether these fall within the allowable expenses)
● Equipment service contracts
● Construction or renovation costs
● Tuition
● Rent for laboratory/office space
● Expenses such as Data Network Recharges and Computing and communication device support services. However, data sharing and/or data storage for imaging, sequencing, and other study data is allowed
● General liability insurances, such as GAEL
● The Alzheimer’s Association Medical and Scientific Advisory Group (MSAG) and the International Research Grant Program (IRGP) Council members are allowed to be key personnel or collaborators on projects, however they are not allowed to receive any salary or compensation. A complete list of MSAG and IRGP Council members can be found on our website alz.org/grants

PROPOSAL SUBMISSION PROCEDURES

1. **Letter of Intent Submission**

The first step in applying to the Alzheimer's Association for any research grant is to create and submit a Letter of Intent (LOI) through the online application system at [http://proposalcentral.com](http://proposalcentral.com). Applications will not be accepted without an approved LOI. First-time users must register and fill out a Professional Profile to begin the LOI/application process. **The LOI and completed application must be submitted by a single Principal Investigator (PI). Applicants must submit a LOI for the current active cycle, NO EXCEPTIONS.** All LOIs must be approved or rejected in the current grant cycle. Hard copies or emails of the LOI will not be accepted. The purpose of the LOI is to ensure that all applicants are eligible for the Zenith competition and to assist Association staff in planning for peer reviews. **LOIs will not be accepted after the deadline date. No exceptions will be made.** The applicant is responsible for adhering to the space limitations (described below) and any decision regarding a LOI will be evaluated on the submitted information.

The Letter of Intent (LOI) is completed through the online interactive system. Applicants must complete the required tabs and upload any required documents. Some of these required fields are described below:
● Name of the principal investigator
● Contact information for the principal investigator
● Lead institution – applicant must be a full-time employee at time of submission
  *(institution/organization name must be in English)*
● List your current academic ranksetPosition at the time of submission, do not list pending
promotions
- Proposal title
- Area of focus for the submission, such as diverse populations, social and behavioral, or biological (options will be available to choose from within the system)
- Brief project description, including methodology, specific aims, innovation/novelty, and potential impact on Alzheimer’s and all other dementia are required. Each section is limited to 1,000 characters including spaces, and it is the responsibility of the applicant to ensure the space limit is adhered to.
- Employer (institution) Identification Number (EIN) -- must match the EIN listed in the non-profit documentation
- All applicants must include an ORCID ID. This is a required field, you will not be able to submit your LOI without this information.
- Provide a W9 signed and dated by the Signing Official for US entities. For non-US entities provide a W8 signed and dated by the Signing Official. **This document should not contain the applicant’s information.**
- A biosketch is required for the primary applicant only. Additional biosketches can be included at the full application stage. It is highly recommended to use NIH biosketch format
- **Budget details are not required at the LOI stage**
- Additional attachments not specifically outlined above are not allowed and will be removed

Each LOI is evaluated by the Alzheimer’s Association and a select panel of experts to decide whether to triage or invite a full proposal, with special attention given to:
- Innovation/novelty of the proposed project (especially in the context of the PI's recently funded work)
- Alignment with the research priorities of the Alzheimer’s Association
- Impact of project on Alzheimer’s and other dementias
- Evidence of methodological rigor that address the research question(s) being proposed
- Past and potential future contributions of the investigator to Alzheimer’s and other dementia research

**Note: Due to the high volume of submitted Letters of Intent, specific feedback and reviewer comments are not provided at the LOI stage.**

The Alzheimer’s Association requires that all applicants be registered as a reviewer with the Association in order to submit a Letter of Intent. If you submit a Letter of Intent/application and are NOT currently registered as a reviewer, you will be automatically added to the Alzheimer’s Association reviewer roster. **As a requirement of submitting an LOI/application, you agree to review at least one grant proposal within your area of expertise in one of the other funding mechanisms outside of the specific grant program to which you are applying.**

2. **Full Application Submission**

If you are invited to submit a full application, the required materials including the application format, templates, and instructions, will be available online at proposalCENTRAL after your LOI has been approved in the system. The full application must consist of the following documents:

1. Problem Statement (1 page)
2. Work Plan (5 pages)
3. Recruitment Plan (1 page) – if applicable
4. Available Resources & Budget Justification (2 pages)
5. Biosketch(es) – PI/Co-PI/Key personnel – limited to 5 pages each
6. W9 signed and dated by the Signing Official for US entities. For non-US entities, a W8 signed and dated by the Signing Official.
8

7. Data Management and Sharing Plan (1 page)
8. Resubmission Response (1 page) – All resubmissions have the opportunity, if they wish, to provide a one-page summary addressing comments raised by reviewers in a prior review cycle(s).
9. References (3 pages) – use the reference style that is most common in the major journal(s) for your discipline, specialty or sub-specialty.

Applications will be reviewed by Alzheimer’s Association and a select panel of experts with special attention to:
● Significance of the question being studied
● Applicant information
● Quality of the work plan
● Quality and adequacy of available resources and budget
● Impact-Risk of the proposal and how it will add to the field’s overall knowledge and advancement
● Response to prior review (if applicable)

The PI who submits the application must be the same PI who submitted the approved LOI. A LOI submitted on behalf of another applicant or by an administrator will result in a rejected LOI. Once the applicant enters the application system, on-screen instructions will be provided to complete the application process. The application does not need to be completed in one session; a partially completed application can be saved and completed at any time before the deadline.

It is imperative that you proofread your application before submission; you will not be allowed to make any changes to the application after the deadline.

It is the responsibility of the applicant to ensure that:
1. The application is submitted by the receipt date/time deadline. Once submitted, you will receive a confirmation e-mail from proposalCENTRAL that your application was successfully submitted. If you do not receive a confirmation, click the Proposals tab and under the “Status” column make sure it says Submitted and not In Progress which indicates you have not yet submitted your application.
2. The application is complete and accurate before submission. Only a single copy of an application will be accepted. Signatures are not required at the time of submission, the signature page is only used should your institution/organization require signatures; we do not override any institutional policies and/or procedures. Please do not submit the signature page with your application.
3. Revisions, additional materials, letters of collaboration/support and/or reference, manuscripts, appendices, etc., are not allowed, and if attached, will be removed from your application.

ETHICAL/REGULATORY APPROVALS & REPORTING REQUIREMENTS
If selected for funding, the Alzheimer’s Association requires that any necessary ethical and/or regulatory approvals are kept current and also requires specific reporting throughout the lifetime of the award. This includes, but is not limited to, the following:

Animal and Human Subject Assurances, and/or rDNA Certification
Animal welfare and human subject assurances are not required at the time of application. Investigators have up to 90 days after receipt of their award notification to submit these documents. However, the Alzheimer’s Association encourages investigators to initiate their certification applications on a schedule that recognizes that rDNA certification, IRB/IACUC approval at many institutions can take more than 90 days. The Association accepts only certifications that apply specifically to the funded project and must include the name of the awardee. An award letter will not
be issued unless the appropriate certifications are in place and include the name of the awardee within the 90 days from award notification. Clinical trials should be registered at an appropriate trial registry within the first year of the award. Appropriate registries can be found here: https://www.who.int/clinical-trials-registry-platform/network/primary-registries. The trial ID must be included in all publications resulting from the funded research.

**Recruitment Efforts for Clinical Studies**
Projects involving human participants must address the appropriate inclusion or exclusion of individuals in the proposed research project and describe recruitment efforts to represent the community in which the study is planned or being conducted. Prior to distribution of funding, the researcher must provide a description of their recruitment plan, including an outline describing how their recruitment efforts will ensure diversity in their participants (see https://www.nimhd.nih.gov/about/overview/ for NIH operationalization). Recruitment efforts should focus on diversity within key target groups, including a diverse representation of, but not limited to: sex, gender identity, sexual orientation, socioeconomic status, race, and ethnicity. This will be tracked throughout the duration of the grant and continued funding is contingent on applications addressing these goals.

**Annual Scientific and Financial Reports**
Interim Scientific & Financial Reports must be submitted at the end of each reporting period as long as the grant remains active. Final Scientific & Financial Reports must be filed within 90 days of the grant's end date. All reports must be submitted electronically via proposalCENTRAL. The Financial Report must be approved and signed by someone with financial authority in the Office of Research and Sponsored Programs at the recipient’s institution.

**Publications, Presentations and Abstracts**
Electronic copies of publications, presentations and abstracts that report research supported by funds from the Alzheimer's Association must be submitted electronically at the time of publication. These copies will become part of the official file of the grant and will be provided to the Communications Division of the Alzheimer's Association to assist in the efforts to further inform the public about the International Research Grant Program of the Association.

**ADDITIONAL INFORMATION**

**Financial Responsibility**
Checks are awarded to the institution, not to the individual principal investigator. The principal investigator or a first degree relative cannot be listed as the signing official or financial officer, or have checks sent to their attention if awarded.

**Multiple and Overlapping Submissions**
If an applicant submits proposals to different grant competitions in the same grant cycle, each proposal submitted must address a distinctly different topic. Only one proposal will be funded if scores for multiple submissions fall within the funding range of different grant competitions. Applicants cannot submit more than one proposal in the same grant competition—even if the proposals cover distinctly different topics.

**Resubmissions**
Applicants may revise and resubmit an application that was previously submitted for an earlier grant cycle; however, a new LOI is required each year. A current LOI corresponding to the application year
must accompany each application. Revisions of previous submissions will be treated as new applications; however, efforts will be made to provide some continuity in reviews. **Resubmission of a LOI does not guarantee that you will be invited to submit a full application in a future cycle.**

**Review Process Overview**
All proposals are subject to a multi-stage peer-review process carried out through an online system. In the first stage, applications are reviewed and rated by a minimum of three peer scientists with expertise in the proposed area of research; Zenith applications are reviewed by previous Zenith Fellows. Applicants may include recommended reviewers and also have the option to exclude specific reviewers from evaluating their application if a conflict of interest exists. Conflicts of interest include (but are not limited to):

1. The Applicant trained with/or by the Reviewer, or the applicant is using data that was generated and/or is overseen by the Reviewer.
2. The Reviewer published with the Applicant in the last four (4) years. This excludes workshops or large consortia (i.e. ADNI, IGAP, etc).
3. The Reviewer has been a co-investigator on a grant application or award with the Applicant in the last four (4) years.
4. Reviewer has a conceptual difference of opinion with the Applicant that will prevent a fair review.
5. Reviewer will gain financial benefit from the Applicant receiving an award.

The second stage includes further review and discussion of the scores and comments resulting from the initial review process. This second review is carried out by invited review committee members, who also are past or active Zenith Fellows, to ensure fairness and equity in the initial review procedures and make funding recommendations to the Association. Final recommendations from the Zenith Society IRGP Council are shared with the Medical and Scientific Advisory Group (MSAG) and with the Alzheimer’s Association for final approval. Members of the IRGP Council and MSAG are internationally recognized experts with distinguished careers in Alzheimer's and all dementias.

The Zenith Fellows Award includes an extra level of review that engages the Alzheimer’s Association Zenith Society to select final award recipients based on projects in which they are most interested. Many of the Zenith Society members have family and friends affected by Alzheimer’s and other dementia and have a deep commitment to advancing the research.

This multi-stage process is central to our award decisions and is designed to ensure both scientific rigor and fairness in the review of all submitted applications.

**Appeals of Scientific Peer-Review**
To maintain a fair and rigorous review system, the Alzheimer’s Association has established a process for appeal of funding decisions. An appeal is intended to address extraordinary circumstances. Appropriate reasons for initiating an appeal might include:

- Evidence that a reviewer has an undeclared conflict of interest
- An egregious error or misunderstanding in the review process
- Active malfeasance or demonstrable lack of due diligence

The appeal process is not intended to provide a mechanism for routine protest of failure to receive a grant. Disparities in peer reviewers’ enthusiasm for a proposal and the scores they assign are nearly always considered part of the normal variation in human judgment. The Alzheimer’s Association International Research Grant Program is extremely competitive and limited by availability of funds. In recent grant cycles, 10 to 15 percent of full applications have been funded, although about twice that number fall into the “fundable” category based on overall score.
If an applicant believes an extraordinary circumstance has contributed to failure to receive funding, the principal investigator may send a two-page, double-spaced formal letter of appeal (Word document) to grantsappeals@alz.org. Any supporting documents must be submitted as a single PDF. Appeals must be submitted within two weeks from the date your application outcome notification is sent. Notification of action on the appeal will be made via email, usually within 90 days of the appeal deadline.

**Nondiscrimination and Harassment Statement**
The Alzheimer’s Association is committed to providing an environment free from harassment and discrimination. The Alzheimer’s Association strictly prohibits harassment and discrimination based on race; creed; color; religion; sex; sexual orientation; national origin; ancestry; age; veteran status; citizenship status; marital status; physical or mental disabilities; pregnancy, gender identity or expression (including transgender status); genetic information; and any other characteristic protected by federal, state or local law.

This program announcement is posted on the website of the Alzheimer's Association at alz.org/grants.

For additional information, please send all inquiries to grantsapp@alz.org.