Lucidity in Dementia
Pre-Application Webinar
*RFA-AG-20-016 and RFA-AG-20-017*

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Housekeeping

- Use the chat function to send us your questions
- This webinar is being recorded and will be posted on the RFA pre-application information page: https://www.nia.nih.gov/research/dgcg/lucidity-dementia
Natural history of Alzheimer’s disease

Lucidity in dementia

• Working definition:
  – Episode of spontaneous meaningful and relevant communication in an individual with dementia
• May occur over the entire course of disease, from early to end stages
• Focus of these RFAs is on lucidity at a time when the capacity for coherent speech has presumably been lost
• Scientific literature includes “terminal lucidity”, “paradoxical lucidity”, “episodes of lucidity”
Rationale to study lucidity in dementia

• Potential to broaden our conceptual understanding of Alzheimer’s disease and related dementias
  – Current models of progression and functional decline in dementia do not adequately account for spontaneous reversals of cognitive ability, even transiently, in late-stage disease
• Potential to impact on family and caregiver attitudes and behavior toward individuals with dementia
• Potential to advance understanding of personhood throughout the course of dementia
• Potential to address ethical challenges or decisional conflicts after unexpected lucidity
Lucidity in dementia is likely under-reported

- Under-recognition
  - Transient phenomenon
  - Stable patients left alone for long periods of time
  - Lucidity may occur more with family than staff
- Masking by antipsychotics or other medications
- Limited reporting channels for family and caregiver witnesses
- Social desirability bias
Relevant publications

- Follows NIA workshop held June 18-19, 2018
- Open access
- Print version expected in August 2019 issue
- Parallel NIA commentary in press
RFAs

• RFA-AG-20-016: Lucidity in Dementia (R21 Clinical Trial Optional)

• RFA-AG-20-017: Lucidity in Dementia (R21/R33 Clinical Trial Optional)
RFA Purpose

To advance scientific understanding of lucidity in dementia by supporting an initial set of retrospective and/or prospective studies that will lay the groundwork for further research on this topic.
Possible topics include, but are not limited to:

- Qualitative and quantitative studies to inform a conceptual understanding of lucidity in dementia and develop working definitions and assessment tools.
  - Surveys of staff, caregivers, and families about incidence, temporal characteristics, fluctuation pattern, speech content, and antecedent correlates of lucidity (e.g., functional status, medications, behavioral characteristics, genetic factors, ethnic/cultural factors, education, care setting, caregiver interactions/characteristics)
  - Clinimetric and/or psychometric studies

- Testing feasibility of audio ± video capture, activity monitoring, or other sensor-based assessments of patients with dementia for prospective study of lucidity.

- Development of computational linguistic approaches to assess or quantify verbal output as a phenotype of lucidity in dementia.

- Studies to explore ethical issues or decision-making challenges/opportunities for families and caregivers of individuals with dementia who manifest lucid episodes.
Types of possible studies

- Retrospective
- Prospective observational
- Interventional
- New recruitment or ancillary to on-going studies
Additional Resources

Studies and cohorts

• **International Alzheimer’s and Related Dementias Research Portfolio (IADRP)**
• **National Health Aging and Trends Study (NHATS)**
• **Health and Retirement Study (HRS)**
• **Bell et al. 2015 Existing data sets to support studies of dementia or significant cognitive impairment and comorbid chronic conditions. Alzheimer’s & Dementia 11(6):622-638.**

Research Centers and Networks

• **Alzheimer’s Disease Research Centers**
• **Alzheimer’s Clinical Trials Consortium**
Important desirable outcomes from these RFAs include, but are not limited to:

- Evidence-based operational definitions of lucidity in dementia
- Clinimetric or psychometric instruments to assess the occurrence of lucid episodes and important associated dimensions of lucid phenomena
- Real-time audio ± video recordings of lucid episodes across stages of dementia, particularly in late stages
- Tools to quantify verbal output and/or other behavioral evidence of lucidity
- Evidence to support decision-making challenges or ethical discourse associated with lucid episodes in individuals with dementia
- Estimates of incidence of lucid episodes in individuals with dementia according to dementia type, stage of disease, and other important subgroupings
R21/R33 Mechanism

• A phased innovation award mechanism
• R21 phase supports exploratory/developmental activities
• R33 phase supports expanded activities that build on the exploratory/developmental phase
• Both phases must be described in a single application (12-page Research Strategy).
  – Applications describing only one phase will not be accepted.
  – It is expected that R33 aims will be dependent on R21 aims
• Applications should describe a set of milestones to be achieved by the end of the R21 phase
R21/R33 Mechanism, continued

• Prior to the end of the R21 phase, successful awardees will submit a progress report and plans for the R33 phase
  – No additional peer-reviewed application is needed for the R33 phase
  – NIA program staff will evaluate progress vis-à-vis R21 milestones to determine suitability to proceed to the R33 phase
  – Approval to transition to the R33 phase will be based on peer review recommendations of the original application, successful completion of the R21 milestones, NIA program priorities, and availability of funds
Examples of R21/R33 studies

- R21 phase: qualitative studies to identify important features about lucid episodes
- R33 phase: a large survey of formal and informal caregivers to quantify the frequency of these features.

- R21 phase: technology development and initial feasibility testing to record lucid episodes and analyze patterns of speech, activity, and/or other behaviors
- R33 phase: implementation in institutional or home settings to capture lucid episodes more broadly and conduct more detailed analyses.

*These are only examples. Other approaches are also possible.*
# Key Dates

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Date</th>
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<tr>
<td>Earliest submission date</td>
<td>January 3, 2020</td>
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<tr>
<td>Letter of intent due (highly encouraged)</td>
<td>January 3, 2020</td>
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<tr>
<td>Receipt date</td>
<td><strong>February 3, 2020</strong> (but aim to submit at least one week earlier)</td>
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<tr>
<td>Peer review</td>
<td>June-July 2020</td>
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<td>Summary statement released</td>
<td>Within 6 weeks following peer review</td>
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<td>Advisory council</td>
<td>August 2020</td>
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<td>Award</td>
<td>September 2020</td>
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Funding and budget

• NIA has set aside $2M in FY2020 to fund 4-6 awards across both RFA’s

• R21 applications are limited to $275,000 in direct costs over 2 years, with no more than $200,000 in either year

• R21/R33 applications are limited to $499,999 in direct costs per year during the R33 phase
  – Budget limits during the R21 phase are the same as for R21-only applications
  – R21 phase may be 1-2 years; R33 phase may be 3-4 years
  – A full budget format (i.e., not modular) must be used for an R21/R33 application
Grantee meetings

• We anticipate multiple grantees meetings either in-person or by videoconference
• R21 Applicants: budget for participation in one in-person grantees meeting during the first year
  – Applications using modular budgets should simply include travel in the budget justification
• R21/R33 Applicants: budget for one in-person meeting during the first year of the R21 phase and one in-person meeting during the first year of the R33 phase
• Actual dates of in-person meetings will be determined after awards are made; grantees can rebudget travel funds accordingly
• Budgets for each meeting should be sufficient to cover the cost of travel to and from the Washington, DC metropolitan area, two nights' lodging, and per diem.
Award process

• Open competition
• Applications undergo primary peer-review and second-level review by the National Advisory Council on Aging
• NIA selects applications based on:
  – Results of peer review
  – Availability of funds
  – Relevance to program priorities
Should applications focus only on Alzheimer’s dementia?

Not necessarily. We want to understand lucid episodes across a variety of dementia subtypes including Alzheimer’s, vascular, Lewy body, and frontotemporal dementias.

In addition, anecdotal evidence suggests that unexpected lucidity may occur in individuals without dementia but who have other neurological or psychiatric conditions. Inclusion of such populations is permissible for comparison as long as dementia remains a major focus of the application.
Should applications focus only on late-stage dementia?

The main purpose of these RFAs is to understand lucid episodes in individuals with dementia when such episodes occur unexpectedly. Thus, late-stage dementia should be the main focus of applications. However, earlier stages of dementia may also be included for comparison to investigate the breadth of fluctuating lucidity.
Are animal studies to explore potential mechanisms within the scope of these RFAs?

Probably not. These RFAs are intended to support an initial set of studies focusing on lucidity in humans with dementia. If successful, such studies could pave the way for subsequent mechanistic studies in animal models in the future.

If you are unsure about the suitability of a potential project, please contact us.
How should I decide whether to apply for an R21 or an R21/R33?

The R21/R33 mechanism is used to allow for a timely transition from the exploratory/development phase of the project to an expanded or implementation phase. (See examples on slide 16.)

The R21 version would be appropriate when plans for an expanded or implementation phase are not clear at the time of application. Applicants who have a promising idea for an exploratory/developmental project but are uncertain about subsequent steps should consider applying for the R21 version.
I am thinking about applying for the R21/R33 version, but how should I write the R33 aims if I do not know what I will find in the R21 phase?

The aims of the R33 portion of the application should be based on an expectation that the aims of the R21 phase will be achieved. As noted in the RFA, achievement of the R21 aims should be reflected by specific milestones, and NIA program staff will determine whether the milestones have been achieved sufficiently to allow transition to the R33 phase.
Can unspent funds from the R21 phase carry over into the R33 phase?

No, the R21 and R33 phases are two separate awards. All funds from the R21 phase should be spent down before the R33 phase begins.
As an R21/R33 awardee, what happens if I do not complete the R21 phase before the scheduled end of the award period?

Awardees are encouraged to complete each phase during its expected award period. In certain cases, delays may cause a project to extend beyond the award period. Remedies are often available in such cases, and awardees can work with program staff to resolve the issues.
Check the pre-application information page periodically for new FAQs:

https://www.nia.nih.gov/research/dgcn/lucidity-dementia