UsAgainstAlzheimer's

Establishing a Learning System to Improve Diagnosis and Care for Patients with Alzheimer's Disease

Request for Information

May 2022

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1.0 ABOUT USA2

UsAgainstAlzheimer's (UsA2) exists to conquer Alzheimer's disease (AD). Since our founding in 2010, we have worked with numerous organizations around the world to take on the toughest problems in the fight to end AD. Our work is driven by the urgency to find effective treatments and the prevention steps needed to reach the time where no one is lost to Alzheimer's.

We bring all of "Us" together to:

- Improve brain health and promote earlier detection, diagnosis and intervention
- Champion health equity and access for communities of color and women who are disproportionately impacted by the disease
- Advocate for increased research spending that will speed treatments to market
- Drive changes that matter most to people living with the disease and caregivers

UsA2 is a nonprofit, nongovernmental organization under section 501(c)3 of the IRS code, based in Washington, DC. Reflecting UsA2's commitment to research and evidence-based care, the organization is launching the pre-competitive, multi-stakeholder Alzheimer's Disease Evidence Accelerator (ADEA), described in detail below.

2.0 PURPOSE

This RFI seeks information and advice from a broad range of experts and stakeholders to inform the design, development, and implementation of the ADEA. The ADEA will serve two main functions: first, it will convene and support a precompetitive, collaborative forum in which experts and stakeholder can share ideas on how best to generate and share meaningful evidence; and second, it will support the development of a real-world data (RWD) infrastructure to enable the efficient generation and sharing of this evidence.

The focus of this RFI is on the second function of the ADEA, which aims to develop a data and analytics infrastructure to collect, curate, and analyze valid, reliable, actionable RWD to support decisions on the diagnosis and management of patients with AD, including benefits and risks and comparative effectiveness of new AD therapies as they move into the clinic. This system would facilitate the generation of key questions for priority review and, in response, both parallel and aggregated analysis of data contributed through a variety of sources—including by sponsors, clinical registries, health data companies, health plans, payers, and directly by patients—thereby yielding findings that could not be ascertained from individual data sources alone. The protection of patient privacy and adherence to patient-centered data collection principles will be paramount.

The ADEA will support the collection, sharing, and interrogation of RWD via a centralized, coordinated system. This infrastructure will be designed to support high-quality observational studies, prospective comparative studies, and streamlined clinical trials, including large scale pragmatic clinical trials. The system will focus on collecting information with longitudinal follow-up, minimizing the burden associated with data collection and aggregation. As discussed in more detail in the background section below, this broad range of study designs will include those that emerge to address the research questions and study requirements described in the Centers for Medicare and Medicaid Services April 2022 national coverage determination on monoclonal antibodies directed against amyloid for the treatment of AD.

UsA2 views this RFI as an opportunity for interested individuals and organizations to contribute information based on their knowledge and experience. We welcome feedback on all aspects of the ADEA as described above. **Specific questions and issues on which we would like feedback are highlighted below in bold text.** We especially welcome your thoughts on leveraging existing data standards and/or creating new data standards for this project, the applicability and advantage of semantic approaches versus a more traditional relational database approach, use of Natural Language Processing (NLP), and any other modern data science strategies you believe are applicable to this project which will allow the us to achieve the goals and vision of the ADEA.

Following the review of feedback to this RFI, and provided information received supports this path forward, we intend to develop a Request for Proposals (RFP) to design, develop, and manage the ADEA. This RFP would be issued by UsA2, on behalf of ADEA. While we are actively working toward securing the funding necessary to continue toward implementation of the ADEA, this issuance of this RFI does not represent a commitment to future funding of the activities described.

3.0 AUDIENCE

We are requesting information and advice from all relevant experts and stakeholders, with a particular interest in understanding the experience, capabilities, data resources, and other assets of potential collaborators and partners. We are eager to hear from organizations and individuals that develop and maintain real-world data resources and infrastructure and with experience in conducting parallel and aggregated analyses across multiple real world data sets across the entire range of real-world data sources. We are also eager to hear from individuals and organizations with knowledge of all aspects of the diagnosis and management of AD to better understand the types of data needs they may have. In addition, we seek input from the full range of decision makers for this condition, including patients, clinicians, regulators, payers, and policymakers to ensure that the ADEA is designed with a clear understanding of the important questions for which these decision makers need answers.

It is anticipated that the ADEA will require collaboration across a number of partners with complementary expertise, experience, and perspectives and that no single organization will be able to support all of the required components.

4.0 BACKGROUND

The FDA approval of aducanumab (marketed as Aduhelm) in June 2021 marked the beginning of the era of disease-modifying therapies (DMTs) for AD and elevated the importance and urgency for new systems to generate and capture RWD. Aduhelm is an anti-amyloid monoclonal antibody (mAb), and several more mAb therapies are in advanced stages of development. FDA approved Aduhelm using its accelerated approval mechanism, and other disease-modifying therapies under development may also pursue this approval pathway. FDA-mandated post-approval clinical trials to confirm the clinical benefit of any agent approved by accelerated approval will take many years to complete. Real-world evidence (RWE) generated using the latest tools and methods has the potential to provide reliable information complementary to—and potentially faster than—evidence produced through post-approval confirmatory trials.

Medicare's coverage decision on antiamyloid mAbs for the treatment of AD states that any of these drugs approved by the FDA through traditional approval with direct evidence of clinical benefit may be covered under coverage with evidence development (CED). These CED studies can be pragmatic clinical trials or other "prospective comparative studies". Medicare specified that CED studies must address all of the following questions for Medicare beneficiaries with a clinical diagnosis of mild cognitive impairment (MCI) due to AD or mild AD dementia:

1. Does the antiamyloid mAb provide meaningful clinical benefit (i.e., slowing in the decline of cognition and function) in broad community practice?
2. Do benefits, and harms such as brain hemorrhage and edema, associated with use of the antiamyloid mAb, depend on characteristics of patients, treating clinicians, and settings?
3. How do the benefits and harms change over time?

Studies that address these questions and the other CMS requirements could be supported by developing a data platform that facilitates distributed and aggregated analyses across a wide range of data sources, including treatment registries, EHR data, claims, smartphone apps, wearables/sensors, and other potential inputs. A neutral, pre-competitive forum (such as the ADEA) will allow researchers and data holders to work together on learning how to efficiently generate date to address questions that are important to CMS, as well as others that are important for clinicians, patients, and other stakeholders.

Stimulated in part by the emergence of promising therapeutics, it is anticipated that the next five to ten years will be a period of rapid progress in the further development of effective treatments, as well as screening tools, diagnostics, biomarkers, and management strategies for patients with AD. High-quality RWE, in the form of high-quality observational studies, prospective comparative studies, and streamlined clinical trials, including large scale pragmatic clinical trials, can provide the necessary information to inform decisions for clinicians, patients, CMS, FDA, private payers, sponsors and others. To support these developments, there is an urgent need to establish a robust "learning system" that leverages the rich ecosystem of RWD. These data must be valid, reliable, relevant, and high-quality; collected consistently; and analyzed using rigorous methods.

The sources for RWD are already vast. These include the patient's electronic medical records; insurance claims; assessments conducted by the clinician as required for or supported by reimbursement; clinician-, patient-, or caregiver-reported assessments focused on outcomes that matter most to the patient; post-approval, confirmatory clinical trials or registries; other patient registry-type databases (like the Alzheimer's Disease Neuroimaging Initiative and the Brain Health Registry); and, in the near future, a range of digital outcome measures captured through passive, ongoing electronic tracking of, e.g., a patient's voice, physical activity, or social engagement. As new therapies for AD enter the market, the amount of RWD will expand at a rate that is difficult to imagine.

Beginning in early 2021 and in response to the profound shifts in the field, UsA2 commenced a series of efforts to design a framework for a centralized data resource to capture AD RWD from a variety of sources. This framework is needed to assure that RWD inevitably collected and owned by different stakeholders do not become siloed, but rather can be compared, analyzed in similar ways, and, potentially, integrated for more highly powered analytics.

The goal of this work is to create the ADEA to support rapid learning to inform health care decisions made by and for patients with AD. The process to develop the ADEA will be informed by the principles and foundational elements of a Learning Health System outlined in 2016 by senior officials from FDA, CMS, NIH, FDA, and other health agencies.[1] In the Learning System envisioned by these authors, "health-related data are continually generated, updated, and stored in accessible format and linked in ways that facilitate research and collaboration while protecting patients and consumer well-being."

The 'north star' for this work is our desire to maximize every patient's contribution of data. As patients use new therapies and are given the opportunity—or required—to contribute data associated with their clinical outcomes, we see the need and an imperative to assure their data will be shared in a way that accelerates our collective understanding of the science of AD. We believe this vision is and should be shared across the public and private sectors.

5.0 ADEA OBJECTIVES

The ultimate objective of the ADEA is to drive our collective ability to learn more about AD and what treatments work, for whom, when, and why in the real world. The ADEA is intended to enable the collection, coordination, and analysis of RWD at a scale that is adequate to represent the diversity of patients with suspected or confirmed AD, from mild cognitive impairment through severe AD. The initial focus will be on patients with early-stage AD, reflecting the target population for current and emerging disease modifying therapies. The ADEA will include data on both treated and untreated patients. It will serve as a platform for the conduct of high-quality observational studies and streamlined randomized trials, including pragmatic clinical trials and cluster randomized trials. Future applications of this infrastructure will promote evidence generation on all aspects of the diagnosis and management of patients with AD, including the ability to assess new diagnostic tools, biomarkers, care pathways, and quality of care.

[1] Califf, Robert M., et al. "Transforming evidence generation to support health and health care decisions." *New England Journal of Medicine* 375.24 (2016): 2395-2400.

We anticipate that the ADEA will be developed in phases, with the number of data sources and analytic capabilities expanding over time. Initially, the system will support parallel/distributed analysis (i.e., the implementation of a standardized master RWE protocol) across multiple RWD sources and transition over time to allow more complex analyses, data aggregation approaches, and linkages between data sources. The ADEA will establish standards for data quality and provenance across the diverse data sources to ensure its analyses are usable for evidence-based decision making.

We envision the ADEA supporting data collection, coordination and analytics that will be capable of supporting analysis on topics such as:

- Efficacy and effectiveness of specific therapies, diagnostic tests, and care management strategies on disease progression and patient well-being / quality of life.
- Comparative effectiveness of different therapies, diagnostic tests, and care management strategies.
- Earlier detection of disease and measurement of disease progression, including through changes in biomarkers;
- The role of disease history and biology;
- Impact of new therapies on a range of clinically important outcomes broader than those measured in trials;
- Early and sensitive safety/adverse event monitoring;
- Impacts of therapies in patient subgroups not well represented in trials, specifically with improved understanding of how the risks and benefits of new therapies may differ across subpopulations;
- Patterns of care

Additional details on high-priority research questions are listed in Section 8.0.

Policy considerations may determine that there is a need for infrastructure to support the conduct of real-world, pragmatic, randomized, controlled trials (RCTs) to evaluate and compare mAb drugs for AD. In this case, it would be possible to focus the ADEA development efforts to support these trials in addition to other types of real-world studies.

The conduct of highly efficient pragmatic clinical trials will be enabled by leveraging existing EHR systems, other RWD sources and ePRO instruments. The emphasis would be on extremely simple screening, enrollment and data collection procedures using the latest tools and methods, while still meeting the requirements articulated by CMS in their draft NCD. The ADEA, if appropriate design, could also support the longitudinal data collection that CMS highlighted would be supported after completion of RCTs.

6.0 CORE PRINCIPLES

To emphasize some of the key principles and goals anticipated for the ADEA, we note the following critical features:

- Person-centered data collection: The ADEA would aim to leverage multiple sources of patient health data while ensuring patients retain a central role in allowing access to this data for clinical care, research, and quality improvement purposes. For some sources of RWD where individual patient consent is not feasible, the role of patients in the overall ADEA governance will ensure that appropriate measures are taken to ensure privacy and appropriate use of patient data.

  To ensure that RWD collected on patients with AD is patient-centered and made broadly available for all experts, stakeholders, and decision makers, we feel strongly that patients, caregivers, and patient organizations should play a leadership role in these efforts. Such nonprofit oversight would ensure that all experts, stakeholders, and decision-makers are represented in the governance of these data collection platforms and that decisions and directions are made based on the guiding premise of what is best for—and from the

perspective of—the patient, as opposed, as examples, the efficiencies of the health system, provider convenience, research aspirations, or cost effectiveness.

- Minimize burden: The system will be designed to minimize data collection burden, cost, and care access barriers to participating by patients, caregivers, clinicians, and health systems. By relying on RWD already routinely collected in the context of the delivery of clinical care such as EHR data, claims, and disease registries, additional data collection burden on patients, clinicians and health systems can be minimized.

- Flexibility, ability to evolve with new knowledge – It is anticipated that this system will be designed with the capacity to expand and evolve over time, recognizing that the understanding of the diagnosis and management of AD will change rapidly over the next decade. For that reason, data elements and definitions will inevitably change over time, requiring changes to data collection analytic techniques. The system would be modular, nimble, and expandable to accommodate the addition of new RWD sources as they emerge.

- Data integrity, privacy, and security: The system will be designed to provide robust safeguards for privacy, security, confidentiality, patient/consumer well-being and autonomy. The person(s) and organization(s) building the learning system should have experience with organizational and technical quality, privacy, and security controls commensurate with industry best practice, especially regarding sensitive research data and PHI.

- Public-private sector, pre-competitive collaboration: The ADEA will require the sustained collaboration of multiple experts and stakeholders from the public and private sector. While such collaborative efforts raise significant logistical and financial challenges, the magnitude and urgency of the need to improve care for patients with AD will not be possible through individual, uncoordinated efforts. Without collaborative efforts, patients, family members and caregivers will experience avoidable suffering.

We are interested in hearing feedback from respondents on these principles, and specific experience or capabilities in developing and/or operating real world data infrastructure that is aligned with these principles.

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7.0 VISION / STRUCTURE

The schema in Figure 1 below reflects our initial vision for the structure and functions of the ADEA. It is presented for the purpose of obtaining feedback from experts and stakeholders on the proposed approach, as well as information and advice on how this vision can be implemented. It is our goal to move forward with this collaborative effort on an expedited time frame with core elements of the system ready to begin data collection in Q2/Q3 of 2022. As noted above, we anticipate that the system capabilities will be phased in, expand, and evolve over time.

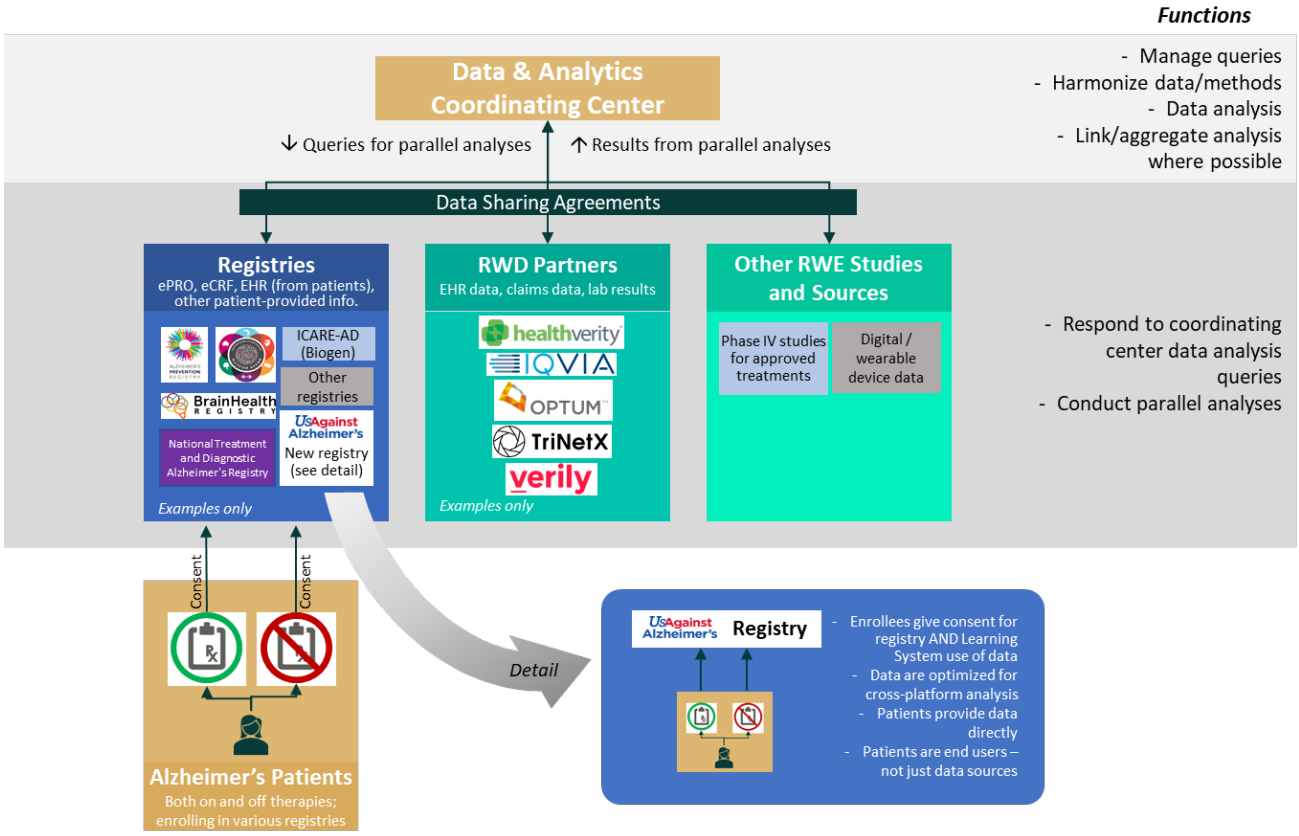

Figure 1: Vision for the ADEA

The ADEA will be a pre-competitive collaboration of researchers, clinicians, industry leaders, patients, data partners, and other stakeholders within a tightly coordinated network, supported by a coordinating center with operational and analytical capabilities. A number of existing data networks may offer useful experience and insights to inform the specific functions, interactions, and capabilities necessary for the efficient operations of the ADEA.

Oversight of the ADEA would be provided by a multi-stakeholder Steering Committee with representatives from patient organizations, data scientists, industry, clinicians, researchers, payers, and regulators. This entity would provide overall strategic direction and be responsible for fundraising to support the operations of the ADEA.

The key components of the ADEA are described below.

7.1 Coordinating Center

The Coordinating Center (CC) would serve four primary functions.

1. Data strategy and curation – Serves as the primary point of contact with the data partners, assisting in recruiting, onboarding, supporting, and retaining these partners; in partnership

with the data partners, will support the development of fit-for-purpose datasets, informed by the highest priority research questions;
2. Analysis intake and prioritization – Sources research questions from applicable parties, identifies areas of overlap/synergy, helps to prioritize analyses for resource allocation and execution;
3. Efficient analysis execution – Provides expertise and capacity to enable analysis execution, supports analysis collaboration from multiple stakeholders, promotes standardization and harmonization that ensures consistent application of high-quality methods, and supports best practices for reporting and publishing results;
4. Coordination and Convening: Assures overall coordination of the ADEA activities involving regular interactions with data partners, researchers, clinical and methods experts and other stakeholders; convenes meetings of ADEA participants and stakeholders to discuss research topics, methods, ongoing projects, and related issues.

The Coordinating Center, in partnership with the collaborating data partners, will develop analytical programs and/or study protocols so that each data partner can evaluate specific research questions using their own data and provide confidential summary information regarding the questions back to the Coordinating Center. Alternatively, the Coordinating Center could run the analytics on data provided by one or more data partners. The CC will develop processes and procedures to ensure efficient and robust distributed and aggregated analyses across the network partners and develop approaches for combining and presenting results from across the network.

We would be interested in feedback on the proposed functions of the Coordinating Center. For example, please comment on whether we should consider having a single organization provide all four CC functions, or whether those could be supported by different organizations with specific expertise that matches one or more of the individual functions described above. It would also be helpful to get recommendations on the most efficient way to conduct parallel analyses while reducing the data flow burden between the coordinating center and data partners, while maintaining a reasonable degree of standardization across queries. Would there be a need to develop or a adopt a Common Data Model in the context of the work of the CC, and if so, how should we approach this? If a common data model is not developed, what other approaches would help to ensure credible distributed and aggregated analyses?

We are also interested in high-level budget estimates to develop and maintain the coordinating center functions described above, ideally for year 1 and for a five-year period.

7.2 Clinical Registries

Individual pharmaceutical companies and non-profits are planning and implementing separate clinical registries that will collect data from health systems and providers prescribing mAbs. Other AD registries already exist and offer good sources of patient data. It is assumed that registry data will be collected from clinicians and patients, using both traditional patient assessment instruments and relying to the extent possible on data from EHRs and ePRO instruments. The ADEA, through the coordinating center or another partner organization, will aim to align efforts across these registries in order to maximize the quality and relevance of the evidence they generate.

UsA2 is interested in developing an EHR-based clinical registry that would collect data on all patients eligible for mAb therapy, whether or not they ultimately receive this treatment. Registry data will be collected from clinicians and patients, using both traditional patient assessment instruments and relying to the extent possible on extracting data generated in the context of routine clinical encounters from EHRs. Additional registry data would be imported from

laboratory, radiology, and administrative data sources, with clinical and functional information obtained through reliance on sensors, smartphones and ePRO instruments. Significant emphasis will be placed on minimizing burden on clinicians and patients associated with study consent and data collection.

We would like to hear from organizations that have developed or plan to develop clinical registries for patients with AD, with as much detail as they are willing to share about their design and implementation plans. We are particularly interested in expressions of interest in participating in a coordinated network of AD registries that would be part of the overall ADEA data platform.

We are also interested in hearing from organizations that would be able to assist UsA2 in designing and implementing an EHR-based clinical registry that leverages other sources of RWD as described above. Please provide a high-level estimate of the costs for this work for a one-year and five-year time period.

7.3 RWD Partners

Additional RWD data for the ADEA would be obtained through partnership with a wide range of organizations that collect health data from in claims, electronic health records (EHRs), laboratory and radiology databases, pharmacy, and other sources.

We are particularly interested in hearing from health systems, data aggregators and other organizations that have existing capability to collect and analyze data elements that are specific to AD, with descriptions of these data assets and analytic capabilities. There may also be a need for the capacity to conduct chart reviews to collect or validate key data elements, and we would be interested in input on the need for this, and organization capabilities to obtain this data.

7.4 Other Clinical Studies and Data Sources

The ADEA would also benefit from access to patient-level, de-identified data from Phase 4 clinical studies, including industry-sponsored confirmatory trials, and high-quality observational studies.

We are aware that there are existing collaborations that support sharing of patient-level data from clinical studies in Alzheimer's disease, such as the Alzheimer's Disease Data Initiative (ADDI), and would appreciate suggestions from ADDI and any similar organizations/initiatives about how this data complement the additional data resources envisioned for the ADEA.

7.5 Distributed RWD Platforms

In the early phase of development of the ADEA, we will focus on establishing the governance structure and functions, along with the coordinating center to help establish working relationships with data holders, identify high priority research questions, develop analysis plans, identify common data elements, and select shared data collection tools (such as the shared ePROs)

In the near term, the ADEA would take advantage of the efficiencies inherent in a distributed, "in-situ" analysis environment, where analyses of data are performed by, or in close partnership with, data-holders such as health systems. We anticipate that in the near-term this distributed model will have several advantages. It will allow holders/owners of data to "come to the table" with confidence that participation in the ADEA will not suggest any change in their platform. It should reduce initial overhead costs and data access challenges associated with data transfer and aggregation or enclave development, while also optimizing the data analysis by developing shared resources such as common variables, common analysis plans, and common research

questions. And, this distributed model will take advantage of design elements adapted, as appropriate, from existing distributed RWD analysis programs, such as FDA's Sentinel Initiative or the COVID-19 Evidence Accelerator.

We would be interested in hearing from respondents their views on what elements of existing public and private sector distributed RWD platforms (e.g., Sentinel, COVID-19 Evidence Accelerator, PCORnet and others) could serve as instructive models to inform the development of the ADEA. In addition, please let us know if you are aware of other efforts to collect and/or analyze real world data from AD patients with whom the ADEA should aim to coordinate or collaborate.

7.6 Phased Approach

Over time, we will identify opportunities to scale up the capabilities of the ADEA, including opportunities to enable large-scale querying and analysis of multiple data sources more efficiently.

We are interested in hearing from those responding to this RFI regarding which ADEA components, functions, capabilities, and activities would be important and feasible to implement in the near term (6-12 months), medium term (1-3 years), and longer term (3 years and beyond). We are particularly interested in hearing views and experience related to the feasibility of creating linkages between data sources as well as data sharing policies, such as willingness to send patient-level datasets to a coordinating center for analysis.

8.0 HIGH-PRIORITY RESEARCH QUESTIONS

The ADEA should be able to answer a broad range of questions that can be addressed with high-quality RWD but may not be produced by traditional Phase 4 clinical trials. Different stakeholders may prioritize these questions differently, and there may be additional important questions not listed here.

Questions would be prioritized based on input across all users, experts, and stakeholders including: Medicare and Medicaid, other public and private payers, patients, the FDA, the pharmaceutical industry and other researchers, and clinicians.

Some illustrative examples of critical questions identified by key stakeholders include:

- Impact on a broader range of clinically important outcomes than those measured in trials:
    - Outcomes that matter most to patients, families, and caregivers (patient-centered outcomes and caregiver burden measures)
    - Additional measures of cognition, quality of life, function
    - Neuropsychiatric symptoms such as agitation, depression, apathy, hallucinations
    - Longer-term effects (beyond typical trial duration)
- Impacts in patient subgroups not well represented in trials:
    - Minority populations, low income, rural populations and others with limited access to clinical trial participation
    - Patients with common comorbidities excluded from trials (e.g., end-stage renal disease (ERSD), chronic renal failure (CRF), diabetes, cardiovascular disease, which often disproportionately affect minority populations)
    - Patients taking widely used medications excluded from trials (e.g., anticoagulation)
- Describing patterns of care:
    - Predictors of disease progression
    - Characteristics of patients treated with mAbs
    - Dosage, frequency and routes of administration in real-world use
    - Rates of amyloid-related imaging abnormalities (ARIA), adverse reactions, serious adverse events, and the potential consequences of discontinuation of therapy

    - Other reasons for discontinuation (in addition to adverse reactions)
    - Determinations of the stage at which it becomes apparent that the drug can be stopped without diminished clinical benefit
- Comparative effectiveness:
    - Information that would help patients, caregivers and clinicians in choosing of the right agent for the right patient

We are interested in getting comments and recommendations from experts and stakeholders on this initial list of potential high priority research questions, with input on both the importance, feasibility, data sources and time frame necessary to address them.

9.0 PATIENT-CENTERED OUTCOMES

To be most relevant to a broad range of clinical and health policy decision makers, the data platform will need to collect health outcomes that are meaningful to patients, providers, caregivers, and is accessible to key decision makers. It will be critical to ensure that these are reliably measured, consistently reported, and validly analyzed in all RWD platforms.

We are interested in learning from the community how best to approach the collection of outcomes data that matters most to patients in all components of the ADEA. We are requesting input on the choice of outcomes to measure, tools and processes for gathering this data, and would like to learn about relevant experience and capabilities for this function.

We recognize that what matters most to patients will likely be reported / generated from patients, caregivers, family/friends. Further, we appreciate the increased focused on assuring that clinical outcome assessments (COAs) used to measure the benefit of new therapies are measures that, in fact, capture outcomes that are clinically meaningful from the perspective of the patient and caregiver. We envision an ADEA dedicated to supporting the understanding of such clinically meaningful outcomes in AD

UsAgainstAlzheimer's, through its AD PACE (Alzheimer's Patient and Caregiver Engagement) initiative, has supported qualitative and quantitative research via one-on-one interviews and then survey research to determine what matters most to people living with Alzheimer's and their caregivers from the earliest stages (pre-symptomatic with evidence of pathology) to the caregivers of those with severe AD (the What Matters Most or WMM Study). This resulted in 42 concepts that were rated as important; the ten most important outcome concepts were concerned in large part with emotional well-being and functioning as it related to staying safe and not being a burden to others. These concepts were then mapped to commonly used, validated COA instruments.

The COA instruments that mapped to the WMM Study outcome concepts that mattered most included:

- ADCS-ADL (17/42 concepts)
- iADRS (15/42 concepts)
- ADCS-ADL-MCI (14/42 concepts)
- ADCOMS (13/42 concepts)
- CDR/CDR-SB (12/42 concepts)

The WMM Study also found that the COA that mapped closest to measuring items reflecting emotional wellbeing was the NPI/NPI-Q (Neuropsychiatric Inventory/Neuropsychiatric Inventory–Questionnaire).

Additional details on the AD PACE project and the instruments above have been published and are available upon request. We believe that a subset of these validated instruments would be a good starting point for collection of prospective, real-world, patient-centered outcomes from patients with

early AD and mild cognitive impairment (MCI). There would need to be additional consideration of data collection burden, frequency of ascertainment and feasibility of collecting these data electronically through web or smartphone-based ePROs.

We are interested in feedback from the community on the optimal choice of validated COAs and other outcomes instruments to include in the ADEA, how best to collect this information, and specifically how to develop further evidence through the ADEA on COAs that capture outcomes that are clinically meaningful from the perspective of the patient and caregiver. We are also eager to learn of other work that has been done to identify critical outcomes to collect for the range of stakeholders and decision makers who would be likely to make use of data and evidence generated through the ADEA.

10.0 INCENTIVES FOR PARTICIPATION

While the potential benefits of the ADEA in generating knowledge are apparent, it will be important to ensure that there are clear incentives for patients, clinicians, health systems, data holders, research organizations and others to participate.

Specifically for data providers, we believe that the following may be incentives to collaborate with the ADEA:

- A shared commitment to the goal of accelerating learning for patients with AD
- Gaining experience with the collection and use of RWD in the context of AD
- Shared learning though collaboration with others that share this interest
- Enriching their data sources by linking to other data with complementary information
- Reputational enhancement by being involved in this high-profile use case for RWD
- Positioning to secure future funding in this space
- Identify potential partners, collaborators, and customers

Many of these motivations will be applicable to other experts and stakeholders.

We believe that there are clear benefits to all stakeholders and would be interested in hearing thoughts from the community about how best to ensure that each stakeholder group has strong motivation for sustained engagement in this work. What features, functions, activities, and approaches are most likely to achieve the desired level of engagement?

11.0 ADDITIONAL TECHNICAL REQUIREMENTS

Each of the five core components identified above in Section 6: Vision / Structure will need to meet certain requirements to achieve the objectives of the ADEA. This section contains a draft set of requirements.

We are interested in hearing feedback from respondents on these requirements, including specific experience and capabilities that would help to achieve them.

11.1 Coordinating Center

The Data and Analytics Coordinating Center should be able to:

- Bring strong perspective and experience in using RWD for outcomes research
- Define minimum dataset requirements for participating in the ADEA, through dialogue with registry and data partners.
- Develop high-quality, rigorous analysis plan(s)
- Establish and disseminate common standards for eCRFs and ePRO data capture
- Manage data queries and data harmonization for analyses.

- Be capable of getting up and running rapidly, while having capacity to scale and evolve over time

Coordinating Center Data Analysis Capabilities should include:

- Expertise in observational research, inferential analysis in distributed environments, epidemiology, biostatistics, and data science.
- Patient data search function with filters and sorting.
- Pre-selected datasets/data views in tabular and graphic formats. Examples may include:
    - Types of treatments used by people in different states of AD
    - Types of treatments used by location (clinic/center, state, county, ZIP code)
    - Outcomes reported by location, patient type (race/ethnicity, age, sex), treatment
    - Treatments use by health plan
- Capability to quickly identify and characterize appropriate data sources (e.g., by product, location, care setting).
- "Cohort builder" function where users can create cohorts of patients based on specific inclusion/exclusion criteria for further exploration
- Data visualization features (graphs, charts)
- Advanced analytic capabilities:
- Descriptive analytics such as treatment patterns, treatment persistence / adherence analyses
- Inferential analysis such as comparative effectiveness / safety analyses
- Predictive analytics

Coordinating Center User Interface should support the following functions. It is anticipated that these capabilities will be phased in over time with increasing complexity that would ultimately include:

- Web-based user interface
- Landing page with login fields and account request field
- Home page with "dashboard" feature
    - Link to My Profile page
    - Announcements/message board
    - Stats on overall data in the system (e.g., number of users by type, number of therapies for which data is captured)
    - List of participating organizations/sponsors (with logos)
- "My Profile" page for users
    - Patients and caregivers: Summary of all data entered about that patient across all data sources.
    - Clinicians: Summary of data added by them (e.g., number of patients, number of EHRs linked)
    - Pharmaceutical companies: Summary of data added by them
- Insurance companies: Summary of data added by them
- Tracking of projects/studies conducted on the platform
- User permissions, including custom data access and analytic functionality by user/user type
- Administrator-only features
    - View of requested new accounts with option to approve.
    - Ability to change view, add, and edit permissions for all existing users.
    - View list of all datasets (manually added and automated linkages) currently in the tool.
    - Manually upload datasets.
    - Add/remove automated linkages to external datasets.

We invite comments on whether it would be feasible and desirable to provide patients and caregivers might with access to ADEA data, and suggestions on what data would

be most useful, how it should be presented, and any helpful existing examples (e.g., Patients Like Me).

11.2 Registries

11.2.1 Clinical Registries

Clinical registries participating in the ADEA should be able to:

- Participate in distributed analyses in collaboration with the Coordinating Center.
- Meet the minimum dataset requirements established by the Coordinating Center or partner organization
- Adhere to standards for data quality and traceability, to be developed in partnership with the Coordinating Center.

11.2.2 UsA2 Registry

The UsA2 Registry should be able to:

- Align with standards for integration/harmonization/best practices as defined by the Coordinating Center
- Be capable of getting up and running rapidly, while having capacity to scale and evolve over time
- Be capable of collecting high-quality, patient-level data from multiple sources including:
    - Electronic health records (EHR)
    - Patient- and caregiver-reported information
        - Active reporting: survey responses, PROs, general profile information
        - Passive reporting: Wearable device data
    - Clinician-reported information (to supplement EHR data, as relevant)
    - Clinical trial or confirmatory study data from pharmaceutical companies (if available)
    - Insurance claims data
    - Laboratory data
    - Pharmacy Data
    - Sensors, Wearables, other digital health technologies
    - Imaging
- Support ePRO & patient engagement
    - Single click login
    - User friendly notifications via email & text
    - No app lightweight/device agnostic
- Support compliance with 21 CFR Part 11 and Good Clinical Practice (GCP)
- Be easy and cost-effective to adopt and use; engage patients, caregivers, and clinicians
- For clinicians/providers, the registry should include EHR integration that enhances clinical workflows. For example, a dashboard, launchable from the electronic patient chart that provides detailed patient data, useful visualizations (including patient comparison to population, and decision support tools where applicable), and outcomes reporting. The outcomes reporting should be achievable by pre-populating the registry's electronic Case Report Forms (eCRFs) with existing data from the patient chart and other sources of patient information, with an absolute minimum amount of manual data re-entry. The registry should also support performing electronic Clinician Outcome Assessments (eCOAs) directly from the dashboard.
- For provider IT, privacy, and leadership teams, the registry technology should be lightweight while still providing a high level of integration and automation. Minimizing risk & effort involved with adoption is crucial to success and scalability.
- For patients and caregivers, the registry should include an ePRO & patient engagement tool that is easily accessible to them through a variety of technology

platforms, including web, mobile, email, and SMS, and provides useful content while minimizing the burden of ePRO reporting. Integration with the patient's existing patient portal tied to their Electronic Health Record is important - e.g., any relevant ePRO reporting done via MyChart should be pulled into the registry and not duplicated.
- The registry should implement recognized data elements and eCRF/eCOA/ePRO definitions that have been expert-reviewed, such as CDASH & PROMIS. It must be designed to meet rigorous data compliance, provenance standards (GCP, Part 11). It should be able to easily exchange data with other systems using REST web services APIs and standard data formats such as CDISC's Operational Data Model (ODM). These interfaces, and the system as a whole, should meet the highest standards for security, data privacy, and chain of custody.
- The registry should use proven technology components that have the flexibility to meet the specific needs of UsA2 yet can be deployed rapidly. Ensure minimal or zero use of custom code, but be able to tailor workflows, user interfaces, and data visualizations to the needs of users. Ongoing supportability and maintenance are also crucial.
- Be available as a software platform for sites, programs, and/or partners not having an established platform for data collection and direct patient engagement. Supports ePRO, eCRF and EHR integration.

11.3 Real-World Data Partners (EHR, claims, etc.)

Organizations with access to RWD that partner with the ADEA should be able to:

- Participate in distributed analyses in collaboration with the Coordinating Center.
- Meet the minimum dataset requirements established in cooperation with the Coordinating Center
- Adhere to standards for data quality and traceability, to be developed in partnership with the Coordinating Center.

12.0 DISCLAIMER

The contents and information provided in this RFI are meant to provide general information to parties interested in developing the ADEA. When responding to this RFI, please note the following:

- This RFI is not an offer or a contract
- Responses submitted in response to this RFI become the property of UsA2
- Respondents will not be compensated or reimbursed for any costs incurred as part of the RFI process
- If UsA2 receives and responds to questions from RFI respondents, UsA2 reserves the right to anonymize the questions and make the questions and UsA2's responses available to all respondents
- Responses to RFIs should contain only high-level discussions of product development efforts and should not contain trade secrets or confidential information. UsA2 does not make any confidentiality commitments with respect to RFI responses but agrees not to publicly distribute RFI responses outside of UsA2 or share RFI responses with other respondents.
- UsA2 is not obligated to contract for any of the products or services described in this RFI
- UsA2 reserves the right to modify or cancel this RFI at any time

13.0 RESPONSE SUBMISSION INSTRUCTIONS

UsA2 views this RFI as an opportunity for interested individuals and organizations to contribute information based on their knowledge and experience. We welcome feedback on all aspects of the ADEA as described above.

Prospective respondents may submit questions to UsA2 in writing by May 20, 2022. UsA2 will compile, anonymize, and respond to all questions and distribute the list of questions and responses to all prospective respondents by June 3, 2022.

Please submit responses to this RFI as a PDF emailed to ADEA@usagainstalzheimers.org by June 17, 2022 with "ADEA RFI Response" included in the email subject line. Responses should not exceed 10 single-sided pages (single-spaced, 12-point font minimum). Brevity and structured format, such as bulleted items, are encouraged. All information must be furnished in writing. UsA2 will provide confirmation of response submission, but respondents will not receive individualized feedback.

13.1 RFI Contact Information

All questions and inquiries regarding this RFI should be directed to:

Russ Paulsen
Chief Operating Officer
UsAgainstAlzheimer's
Cc: ADEA@usagainstalzheimers.org

13.2 Anticipated Time Frames for Evaluation and Selection Process

Issue RFI..... May 4, 2022

Questions on RFI due..... May 20, 2022

UsA2 responds to any RFI questions..... June 3, 2022

Responses from potential collaborators due..... June 17, 2022

Invitations sent to respondents for presentation..... June 30, 2022

Presentation to UsA2 by respondents..... July 2022

**Dates subject to change without notice*