On behalf of UsAgainstAlzheimer's, the Global CEO Initiative on Alzheimer's Disease (CEOi) and the additional signatory individuals and organizations listed below, we thank the U.S. Preventive Services Task Force (USPSTF) for the opportunity to provide comments on the Draft Research Plan for Cognitive Impairment Screening in Older Adults. We deeply appreciate the USPSTF's commitment to reviewing the evidence on cognitive screening and its potential to improve outcomes for millions of older Americans and their families.

Alzheimer's disease is one of the most significant public health crises in the U.S., threatening millions of Americans. Alarming new research estimates a 42% lifetime risk of Alzheimer's and dementia after age 55, with new U.S. cases growing to 1 million each year by 2060. Early detection of cognitive impairment—particularly mild cognitive impairment (MCI), which can be an early stage of Alzheimer's or other forms of dementia—is essential. Timely identification opens the door to planning, support, lifestyle changes, and, increasingly, the possibility of accessing treatments or participating in clinical research. Furthermore, new care systems like the U.S. Centers for Medicare and Medicaid Services (CMS) GUIDE Model provide better access to, and coordination of, care for patients across the country.

The USPSTF plays a critical role in shaping preventive care practices, and its study of this issue has the potential to influence the ability of patients to access the interventions and care they need to delay onset and improve outcomes. We applaud the Task Force for revisiting this important question.

UsAgainstAlzheimer's and CEOi are uniquely positioned to advance the fight against Alzheimer's by getting people the care they need and bringing unparalleled expertise to the table**.** Our goal is clear: to end Alzheimer's through prevention, early detection, and ensuring access to effective treatments.

UsAgainstAlzheimer's has made significant strides by engaging directly with patients and those at risk through innovative tools like the BrainGuide™ digital platform and the A-LIST® community. These initiatives provide invaluable insights into patient needs and deliver critical support, helping individuals navigate their cognitive health journeys. CEOi has assembled more than 200 cross-sector experts to establish performance standards and clinical practice recommendations for emerging technologies like Blood-Based Biomarkers (BBMs) and Digital Cognitive Assessments (DCAs). These tools are transforming the diagnostic landscape, making early and accurate detection more accessible.

Together, UsAgainstAlzheimer's and CEOi are dedicated to ensuring that individuals and families receive the care and support they deserve, backed by the expertise necessary to shape effective solutions and advocate for progress. Our comments focus on several areas

of the draft research plan where we believe additional clarity, refinement, or emphasis is warranted. Key themes to our comments include:

- **Updates to the Analytical Framework to Account for Additional Evaluation of the Etiology of Cognitive Impairment:** The diagnostic and care journey for Cognitive Impairment is complex, with multiple etiologies and steps required before treatment or interventions begins. We support expanding the proposed analytical framework to include additional step(s) to identify the cause of Cognitive Impairment which can tailor more effective interventions for both reversible/addressable and neurodegenerative causes.
- **Inclusion of Blood-Based Biomarkers to Support Etiological Diagnosis:** While not recommended for broad screening at present, dramatic advancements since the prior USPSTF recommendations have been made in the science and adoption of BBMs in identifying the right individuals for further testing and/or treatment. We believe these should be specifically included in the research plan as an intervention along with both pharmacological and non-pharmacological options.
- **Inclusion of Digital Cognitive Assessments as Screening Tools:** Similar to BBMs, significant progress has been made in the development and adoption of DCAs. These tools are increasingly providing practical means for early detection of cognitive impairments. As such we believe they should be explicitly included in the analysis as a screening tool.
- **Inclusion of Paid Family Members as Part of Population Focus:** For those individuals living with dementia, family members who serve as either paid or unpaid caregivers are a vital and important part of the diagnostic and treatment journey. We would suggest any family members/ friends be included, regardless of whether they are paid.

The last several years have seen tremendous advancements in the diagnosis and treatment of patients with Alzheimer's disease. Identifying the disease early provides more time for affected individuals and their families to make informed decisions, longer windows to adopt lifestyle interventions that can impact the course of the disease, and improved safety and disease-modifying treatment options for those who are appropriate candidates for pharmaceutical intervention. Taken together, we see significant value for patients to be screened and identified early in the course of the disease.

We thank the Task Force for its thoughtful work and look forward to contributing to this important effort.

Signed,

UsAgainstAlzheimer's, CEOi and the below listed collaborators and signatories:

Individuals (alphabetical)

Andrea Bozoki, *Professor of Neurology, University of North Carolina Chapel Hill*
Anupam Raina, *Postdoc, University of Alabama at Birmingham*
Daniel C. Potts, MD, FAAN, *Neurologist, Cognitive Dynamics Foundation*
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Maryam Beigi, *Medical Doctor, Neurologist, UCLA*
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Michael Hornbecker, MD, *US Fellowship Lead, Davos Alzheimer's Collaborative*
Nancy A Hodgson, *Professor, University of Pennsylvania*
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R. Scott Turner, *Georgetown University Memory Disorders Program*
Sam Gandy, *Professor, Mount Sinai*
Soo Borson, *Professor, Keck USC School of Medicine*
Suzanne Schindler, *Associate Professor of Neurology, Washington University School of Medicine*
Takashi Amano, *Assistant Professor, Rutgers University*

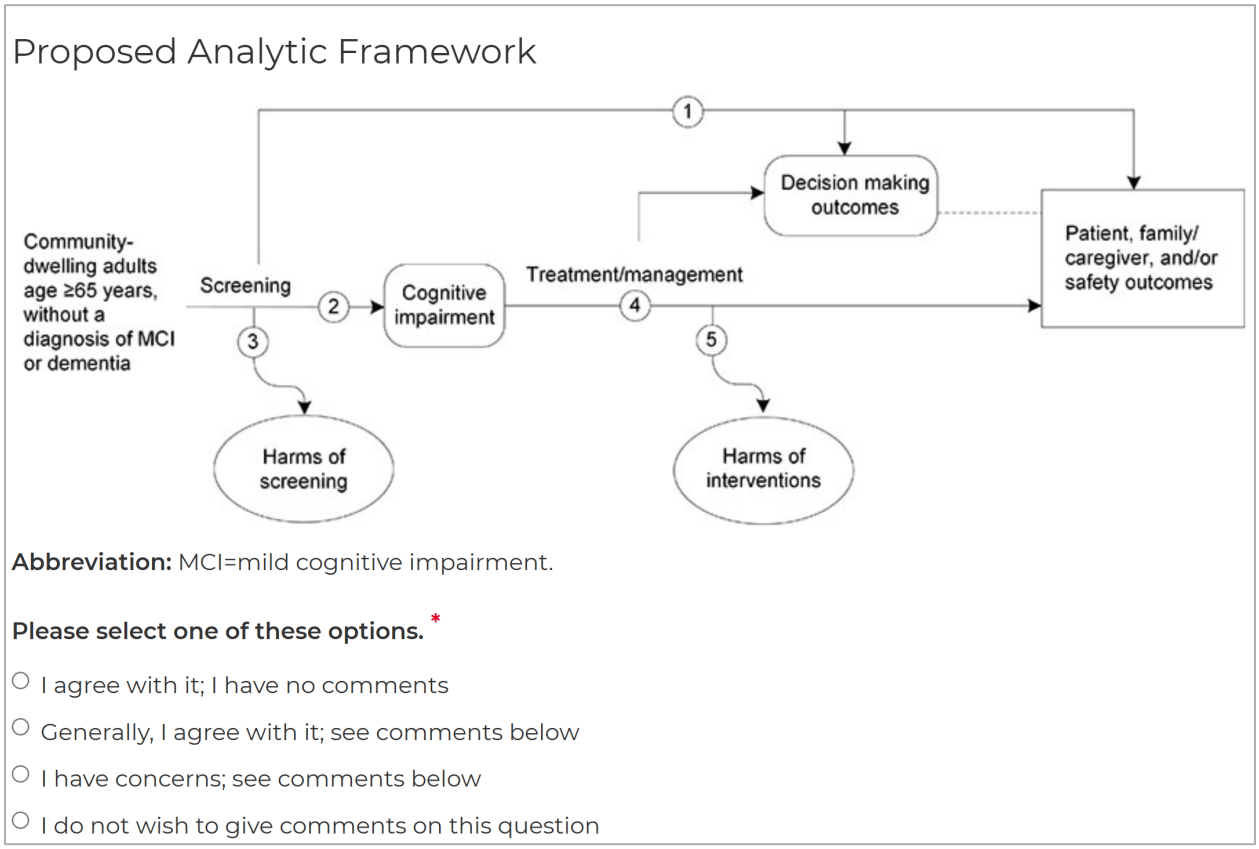
Organizations (alphabetical)

Alliance for Patient Access
Alzheimer's Disease Resource Center, Inc.
Alzheimer's Los Angeles
Alzheimer's Orange County
Alzheon
American Medical Women's Association
Caregiver Action Network
CaringKind, the Heart of Alzheimer's Caregiving

Davos Alzheimer's Collaborative
Gerontological Society of America
Global Alzheimer's Platform Foundation
Infusion Access Foundation
Lewy Body Dementia Resource Center
Lupus and Allied Diseases Association, Inc.
Marymount University
National Association of Activity Professionals
National Certification Council for Activity Professionals (NCCAP)
Nevada Chronic Care Collaborative
Noah Homes Inc
Pentara
Positrigo, Inc
Second Wind Dreams, Inc.
The Balm In Gilead, Inc.
Voices of Alzheimer's
Women's Brain Project

Point by Point Feedback

1. Analytical Framework: Website Prompt



Proposed Multiple Choice Response: I have concerns; see comments below

Proposed Commentary: The diagnostic and care journey for patients with cognitive impairment is complex and multifaceted. We believe that additional features and nuances to the proposed analytical framework are warranted and support the comments of partners to this same effect.

Most notably, "Cognitive Impairment" has many etiologies, and—just as many of the other screenings USPSTF has evaluated—there should be additional diagnostic steps that take place before "treatment and management" begins. Omitting this step could distort the Task Force's understanding of benefits versus risks.

Here, advancements in technologies like Blood-Based Biomarkers (BBMs) have been significant since the previous USPSTF study on screening for Cognitive Impairment. We support the inclusion of additional steps / interventions in this pathway and the associated parts of the research plan as noted in our comments in further sections. Lung cancer and other frameworks may provide a useful model here.

It is important to note that there are various “reversible” or “addressable” causes of Cognitive Impairment (e.g., vitamin deficiency, thyroid disorders, infection, depression, medication side effects, insomnia, etc.). Screening for Cognitive Impairment and further etiological testing can help identify and address these causes.

2. Key Question 1: Website Prompt

Proposed Key Question 1

Does screening for cognitive impairment in community-dwelling older adults improve decision making, patient, family/caregiver, or safety outcomes?

Please select one of these options. *

- ○ I agree with it; I have no comments
- ○ Generally, I agree with it; see comments below
- ○ I have concerns; see comments below
- ○ I do not wish to give comments on this question

Proposed Multiple Choice Response: I agree with it, I have no comments.

Proposed Commentary: N/A

3. Key Question 2: Website Prompt

Proposed Key Question 2

What is the accuracy of screening instruments to detect cognitive impairment in community-dwelling older adults?

Please select one of these options. *

- ○ I agree with it; I have no comments
- ○ Generally, I agree with it; see comments below
- ○ I have concerns; see comments below
- ○ I do not wish to give comments on this question

Proposed Multiple Choice Response: I agree with it, I have no comments.

Proposed Commentary: N/A

4. Key Question 3: Website Prompt

Proposed Key Question 3

What are the harms of screening for cognitive impairment in community-dwelling older adults?

Please select one of these options. *

- ○ I agree with it; I have no comments
- ○ Generally, I agree with it; see comments below
- ○ I have concerns; see comments below
- ○ I do not wish to give comments on this question

Proposed Multiple Choice Response: I agree with it, I have no comments.

Proposed Commentary: N/A

5. Key Question 4: Website Prompt

Proposed Key Question 4

Do interventions for cognitive impairment in community-dwelling older adults improve decision making, patient, family/caregiver, or safety outcomes?

Please select one of these options. *

- ○ I agree with it; I have no comments
- ○ Generally, I agree with it; see comments below
- ○ I have concerns; see comments below
- ○ I do not wish to give comments on this question

Proposed Multiple Choice Response: I have concerns, see comments below

Proposed Commentary: We suggest that the phrase “the underlying cause(s) of” be inserted into the question so that it reads: Do interventions for the underlying cause(s) of cognitive impairment in community-dwelling older adults improve decision making, patient, family/caregiver, or safety outcomes?

As noted above, there are numerous different etiologies of cognitive impairment and with better mechanisms to test and treat specific causes we believe this nuance is important.

5. Key Question 5: Website Prompt

Proposed Key Question 5

What are the harms of interventions for cognitive impairment in community-dwelling older adults?

Please select one of these options. *

- ○ I agree with it; I have no comments
- ○ Generally, I agree with it; see comments below
- ○ I have concerns; see comments below
- ○ I do not wish to give comments on this question

Proposed Commentary: We suggest that the phrase "the underlying cause(s) of" be inserted into the question so that it reads: What are the harms of interventions for the underlying cause(s) of cognitive impairment in community-dwelling older adults?

As noted above, there are numerous different etiologies of cognitive impairment and with better mechanisms to test and treat specific causes we believe this nuance is important.

6. Contextual Question 1: Website Prompt

Note: this question has the following note on the methodology: Contextual questions will not be systematically reviewed and are not shown in the Analytic Framework.

Proposed Contextual Question 1

Does a diagnosis of cognitive impairment improve patient, family/caregiver, or clinician decision making?

Please select one of these options. *

- ○ I agree with it; I have no comments
- ○ Generally, I agree with it; see comments below
- ○ I have concerns; see comments below
- ○ I do not wish to give comments on this question

Proposed Multiple Choice Response: I have concerns; see comments below.

Proposed Commentary: As noted elsewhere in our commentary, we believe there is value to adding additional granularity to the analytical framework which would include the etiologic diagnosis of Cognitive Impairment. Consistent with this recommendation, it would be appropriate to add a second contextual question akin to the one the USPSTF presently proposes. Proposed wording for such a question is provided below:

Does an etiologic diagnosis improve patient, family/caregiver, or clinician decision making?

7. Variation in Evidence: Website Prompt

Proposed Approach to Assessing Variation in Evidence Across Populations

For all Key Questions, we will describe the population and intervention characteristics of the included studies to assess the degree to which the evidence is representative of the U.S. population. Further, we will characterize the extent to which interventions are tailored to meet the needs of specific populations. We will also analyze the benefits and harms of interventions by populations to the extent that this is reported in the literature. Age may be an important characteristic as it may influence generalizability of treatment trials to screen-detected populations.

Please select one of these options. *

- ○ I agree with it; I have no comments
- ○ Generally, I agree with it; see comments below
- ○ I have concerns; see comments below
- ○ I do not wish to give comments on this question

Proposed Multiple Choice Response: I agree with it, I have no comments

Proposed Commentary: N/A

8. Research Approach: Website Prompt (Multiple Pages)

Proposed Research Approach

The Proposed Research Approach identifies the study characteristics and criteria that the Evidence-based Practice Center will use to search for publications and to determine whether identified studies should be included or excluded from the Evidence Review. Criteria are overarching as well as specific to each of the key questions.

	Included	Excluded
Condition	**KQs 1–3:** Any cognitive impairment (mild cognitive impairment or dementia) **KQs 4, 5:** Mild cognitive impairment or mild to moderate dementia	**KQs 4, 5:** Severe dementia
Populations	**KQs 1–3:** Community-dwelling older adults (including those residing in independent and assisted living facilities) age ≥65 years without a current diagnosis of mild cognitive impairment or dementia **KQs 4, 5:** Community-dwelling older adults (including those residing in independent and assisted living facilities) age ≥65 years with a current diagnosis of mild cognitive impairment or dementia; informal caregivers taking some responsibility for the care of the patient, such as a spouse, partner, relative, or friend	• Studies comprised exclusively or predominantly of persons diagnosed with depression or psychosis, alcohol use disorder, HIV/AIDS, Down syndrome, posttraumatic brain injury, metabolic disorders, Parkinson's disease, Huntington's disease, or stroke • Persons living in special settings outside of the community (e.g., hospitals, skilled nursing facilities, rehabilitation facilities, subacute care facilities) • Professional caregivers who are formally or professionally trained and paid a salary
Settings	Primary care outpatient settings (ambulatory care), home, and independent and assisted living facilities	**All KQs:** Hospitals, skilled nursing facilities, rehabilitation facilities, subacute care facilities, emergency departments, or other settings not generalizable to primary care **KQs 1–3:** Studies in which participants are recruited from memory, dementia, geropsychiatry, or neurology clinics
Screening	Primary care–feasible screening instruments administered to the patient: • Very brief instruments (administered in <5 minutes) reported in two or more studies • Commonly used and studied brief instruments (administered in ≤10 minutes): Montreal Cognitive Assessment, Mini-Mental State Examination	Biomarkers (cerebrospinal fluid, blood plasma, urine sampling) or imaging (computed tomography, magnetic resonance imaging, positron emission tomography) Instruments not aimed at assessing cognitive function (e.g., IADLs), subjective report, or informant report

Interventions	*Patient pharmacologic interventions:*
	
	Pharmacologic interventions with a primary aim to reduce decline or improve patient cognitive function
	
	• Pharmacotherapy approved by the U.S. Food and Drug Administration (alone or in combination) for the treatment of mild and/or moderate dementia, included but not limited to:
	  ◦ Amyloid-targeted therapies (lecanemab, donanemab)
	  ◦ Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine)
	  ◦ NMDA (N-methyl-D-aspartate) receptor antagonists (memantine)
	• Cessation of medications that may be contributing to cognitive impairment
	
	Patient nonpharmacologic interventions:
	
	• Nonpharmacologic interventions aimed primarily at the patient:
	  ◦ Cognitive training, rehabilitation, or stimulation, with or without motor skills training interventions
	  ◦ Exercise interventions
	  ◦ Nutrition and lifestyle counseling interventions
	  ◦ Multidisciplinary and/or multicomponent care interventions involving assessment and care coordination
	  ◦ Education-only interventions
	
	Caregiver interventions:
	
	Nonpharmacologic interventions aimed primarily at the caregiver or caregiver-patient dyad
		• Interventions aimed at behavioral and psychological symptom management of dementia (such as behavioral treatments, antipsychotics, antiepileptics, and antidepressants for agitation, psychosis, depression, insomnia)
		• Cognitive impairment pharmacotherapies discontinued by the manufacturer (tacrine, aducanumab)
		• Medications used to treat cerebrovascular disease (e.g., antiplatelet medications, antihypertension medications, HMG-CoA reductase inhibitors)
		• Nonsteroidal anti-inflammatory drugs
		• Gonadal steroids
		• Vitamins, minerals, and antioxidants
		• Herbal supplements
		• Medical foods or fluids or nutrition therapy (e.g., meal replacement therapy)
		• Interventions aimed at primary prevention of cognitive impairment in those with baseline normal cognition
		• Respite care or day care interventions

Comparisons	**KQs 1, 3:** No screening, usual care **KQ 2:** Reference standard (clinical assessment or neuropsychologic testing with explicit diagnostic criteria) **KQs 3–5:** • No intervention • Usual care • Wait list • Attention control • Minimal intervention	**KQs 4, 5:** Active intervention

Outcomes	**KQs 1, 4:** *Decision making outcomes:* • Goal-concordant care: Healthcare, legal, and financial planning and decision making (e.g., advanced directives); safety planning; living arrangements *Patient-related outcomes:* • Health-related quality of life • Incident dementia • Overall dementia severity • Cognitive function • Function: ADLs, IADLs, global function • Dementia-related symptoms/behaviors • Safety (falls, motor vehicle and other accidents, medication adherence/compliance/errors) • Unanticipated healthcare utilization (emergency use/hospitalizations) • Institutionalizations/nursing home admissions *Family/caregiver-related outcomes:* (a priori defined as primary or secondary outcomes in the trial) • Health-related quality of life • Global stress/distress • Caregiver burden • Depression • Anxiety *Societal outcomes*: • Safety outcomes **KQ 2:** Sensitivity, specificity, or contingency table data allowing for calculation of sensitivity or specificity **KQ 3:** Psychological harms (depression, anxiety, quality of life) and harms due to labeling (insurance status, driving privileges, independence) **KQ 5:** Serious adverse events (e.g., death, serious adverse drug reactions), total adverse reactions from medications, withdrawals due to adverse events, and unexpected medical attention (e.g., emergency department visits, hospitalizations)	**KQs 1, 4:** *Decision making outcomes:* Cost-related outcomes *Patient-related outcomes:* Cost-related outcomes; patient satisfaction (other than health-related quality of life); biomarker protein levels, brain matter volume, and brain cell activity level; function markers (e.g., Timed Up and Go Test, 6-meter timed walk, Functional Reach Test) *Family/caregiver-related outcomes:* Cost-related outcomes; family/caregiver satisfaction (other than caregiver burden and health-related quality of life) *Societal outcomes:* Cost-related outcomes **KQs 3, 5:** Patient or family/caregiver dissatisfaction (other than psychological harms or patient adherence)

Timing of outcome assessment	**KQs 1, 4:** ≥3 months after baseline **KQs 3, 5:** No minimum followup	**KQs 1, 4:** <3 months after baseline
Countries	Studies conducted in countries categorized as "Very High" on the 2022 Human Development Index (as defined by the United Nations Development Programme)	Studies conducted in countries that are not categorized as "Very High" on the 2022 Human Development Index
Study designs	**KQs 1:** Randomized, controlled trials; nonrandomized controlled studies **KQ 2:** Diagnostic accuracy studies **KQs 3:** Randomized, controlled trials; nonrandomized controlled studies **KQ4:** Randomized, controlled trials **KQ 5:** Randomized, controlled trials included in KQ4; large observational studies for pharmacotherapies	**KQs 1, 4:** Observational studies **KQ 2:** Case-control studies **KQs 3, 5:** Case series, case reports
Language	English	Languages other than English
Study quality	Studies at low or moderate risk of bias	Studies at high risk of bias (according to design-specific USPSTF criteria)

Abbreviations: ADLs=activities of daily living; IADLs=independent activities of daily living; KQ=key question; USPSTF=U.S. Preventive Services Task Force.

Please select one of these options. *

- ○ I agree with it; I have no comments
- ○ Generally, I agree with it; see comments below
- ○ I have concerns; see comments below
- ○ I do not wish to give comments on this question

Proposed Multiple Choice Response: I have concerns, see comments below

Proposed Commentary: There are several areas that we believe should be revised in the Research Approach section. In order as they appear they include:

- **Condition:** As noted, while we understand the focus of this research is on various forms of dementia, we would note there are simple, effective interventions that address what are commonly referred to as "reversible" or "addressable" causes of cognitive impairment that should generally be acknowledge even if not formally part of the research plan.
- **Population:** Individuals with dementia may have a caregiver who is both a family member or close friend, and paid for their services if appropriately trained. We would suggest any family members/ friends be included, regardless of whether they are paid.

Additionally, while we understand the focus of this effort is on screening individuals over the age of 65, we suggest that the Taskforce consider studies where the inclusion criteria may have included patients younger than 65 but the average patient age is over 65. For some studies, the bulk of the patients may be over the age of 65 and specific subgroup analysis may not be available excluding patients below the age of 65.

- **Screening:** The proposed wording is slightly ambiguous as to whether additional screening measures beyond those specifically named would also be included. We suggest that it be made clear that the tests named (i.e., Montreal Cognitive Assessment and Mini-Mental State Examination) are not the only tests that will be included. Specifically, there have been rapid developments as it relates to the availability of so-called Digital Cognitive Assessment that can provide comparable sensitivity and specificity to existing tools while addressing access, logistics, or other rater derived shortcomings of existing tests.

  Additionally, we would also suggest that the specific time requirements be excluded or relaxed in the specifications as tests may be administered in different healthcare settings that could potentially allow for greater testing time windows.
- **Interventions:** As noted in our earlier comments, we believe there is significant value for including information about the additional diagnostic steps following identification of Cognitive Impairment that be included in the patient journey.

  Specifically, Blood-Based Biomarkers and other tools are rapidly being integrated into clinical care to aid in the diagnosis of Alzheimer's Disease. While we agree with the Taskforce's plan to exclude these tools as a screening mechanism, we do believe they should be included as a specific intervention separate from pharmacological and non-pharmacological interventions listed.

  There are also interventions such as shunts for normal pressure hydrocephalus or vitamin supplements for B-12 deficiencies that may address a reversible / addressable cause of Cognitive Impairment. As such, we believe those should not be excluded if they are used in the context of a specific deficiency.
- **Outcomes:** As screening for Cognitive Impairment can help detect pathology earlier in the course of disease, we ask the Taskforce to consider the outcomes of treatments specifically in patients who receive the treatment earlier stages of disease. This would be aided by including data in patients younger than the age 65 where relevant.

- **Study Designs:** While we understand the Taskforce's emphasis on randomized controlled studies, the timeline for Cognitive Impairment progression to MCI and dementia can oftentimes be long. As such observational studies may provide useful data points secondary to RCT based evidence. For instance, there may be situations where follow-on post-marketing studies are conducted after an initial RCT is complete that tracks outcomes for extended time horizons – in some cases after all participants are given the option to be included in the treatment arm. These studies may provide valuable insights and we believe should be included.