PhysiciansCommittee
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January 27, 2017
Advisory Council on Alzheimer's Research, Care and Services

Assistant Secretary for Planning and Evaluation, Room 415F
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, D.C. 20201

Sent by email (napa@hhs.gov)

Re: Public Comment on Clinical Trials for Advisory Council Meeting #23, February 3, 2017

I am here on behalf of the Physicians Committee for Responsible Medicine, a Washington DC-based non-profit organization working to advance medical research. Thank you to the NAPA Advisory Council and to all those working tirelessly on the National Alzheimer's Plan to lead the growing efforts to halt the devastating effects of dementia on individuals and our communities.

Although evolution of the Alzheimer's disease and related dementias (AD/ADRD) clinical trials play a central role in achieving the goal of preventing and effectively treating AD/ADRD by 2025, we urge the Council to recognize a number of major caveats and gaps with the current approaches. In particular, there are four major factors in the current drug development pipeline that have and will continue to impede the development of effective disease-modifying treatments:

1) **Preclinical Validity Cannot Hinge on Animal Models:** Most current clinical trials initiate from testing drug candidates in genetically-engineered animal models and so do not accurately capture the human disease. In addition, physiological differences between species confound the roles of intrinsic mechanisms essential to the human disease process. Hence, treatments found to be effective in these animal models are often found to be ineffective in human clinical trials. Preclinical research must accelerate emphasis of human-based approaches. (See: http://www.altex.ch/All-issues/Issue.50.html?iid=150&aid=4).

2) **Related Conditions Should Not Be Part of Exclusion Criteria:** AD/ADRD is often associated with chronic conditions such as cerebrovascular disease, type II diabetes, cardiovascular disease, and hypertension. However, with the exception of studies that explicitly search for links, these important comorbid conditions are too often part of exclusion criteria from many AD/ADRD clinical trials. These exclusions bias our science and miss critical opportunities for important therapeutic approaches that can directly address the chronic factors contributing to sporadic AD (see also #4). And they may preclude effective interventions coming out of clinical trials from being broadly applicable to all AD/ADRD patients.

3) **Reduce Reliance of Familial AD factors to Inform Sporadic AD Therapy:** Drug targets for clinical trials are often based on rare genetic defects associated with the inherited form of the disease rather than the chronic form of the disease found in the sporadic AD population commonly associated with lifestyle factors. Moreover, potential drug candidates are often tested in patients with the common form of the disease who may or may not carry the targeted genetic risk factors.

4) **Tackle Lifestyle Factors on Even-Footing with Genetic Risk Factors:** Current AD clinical trials primarily aim to modify the pathology associated with AD/ADRD rather than addressing the important underlying lifestyle factors that have effects -- both positive and negative -- on the prevalence and progression of dementias. While beta-amyloid and tau may be important hallmarks of the disease, they may be only pathological consequences and not causes. Hence, targeting these elements often fails to modify the disease or only temporarily ameliorates the symptoms. In contrast, lifestyle factors such as diet, physical activity, exposures to toxins (e.g. tobacco, air pollution), cognitive and social engagement are powerful modifiers (http://thehill.com/blogs/congress-blog/healthcare/311025-ensuring-the-21st-century-cures-act-ends-alzheimers). Epidemiological studies have shown that these factors can influence both dementia as well as the chronic diseases associated with and likely contributes to AD/ADRD. A shift to clinical trials with increased focus on prevention and intervention in these realms would forward the science greatly as well as improve and save many lives. (http://www.impactjournals.com/oncotarget/index.php?journal=oncotarget&page=article&op=view&path[]=9175)

As the NAPA advisory council works to address the important challenges in clinical trial recruitment, it is essential that the efforts of thousands of patients, caregivers, clinicians and researcher be focused on the most promising targets. Support for future trials based on data derived from humans, preclinical investigation in human-based models, greater prioritization of targeting lifestyle risk factors such as diet will greatly improve our development pipeline for effective interventions to prevent or reverse AD/ADRD in our nation by 2025.

Thank you,

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