Comments on "Workgroup on NAPA's Scientific Agenda for a National Initiative on Alzheimer's Disease

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GENERAL COMMENTS

The International Society for CNS Clinical Trials and Methodology (ISCTM – www.isctm.org) appreciates having an opportunity to review and comment on the Workgroup draft report circulated by the Alzheimer's Association. Recognizing the importance of this document and plan to the public, our patients, clinicians, clinical investigators, scientists, and other stakeholders, ISCTM convened the working group listed above to review and comment on this report. Our Mission Statement demonstrates how closely aligned our activities and interests are with the Alzheimer's Association and NAPA stakeholders:

The International Society for CNS Clinical Trials and Methodology (ISCTM) is a multi-disciplinary independent organization, devoted to promoting advances that address strategic clinical, regulatory, methodological and policy challenges that arise in the development and use of CNS therapeutic agents. This work is accomplished through partnership with persons in academia, industry, government, policy-making, and the public.

In the last year, we have conducted as part of our Semi-Annual Meetings, a research methodologies symposium focusing on the Amyloid Hypothesis, as well as a Public Health Policy to Research Forum focusing on early detection and novel, cost and time efficient, clinical trials designs to assess prevention and disease course modification strategies for Alzheimer's Disease and Schizophrenia . Our meetings are uniquely structured to engage our audience of experts from many disciplines and organizations in a problem-solving mode.

ISCTM recognizes that a great deal of effort has gone into the draft report, and understands that the approaches and recommendations represent the consensus of a distinguished Workgroup. Our Society with its multi-disciplinary approach focusing on research methodologies addresses: early detection and diagnosis; assessment of disease progression; statistical strategies to enhance signal detection; biomarker validation and use; recommendations for cost and time efficient study designs to assess drug and non-drug therapies; and regulatory considerations. The confluence of these interests and the focus of the report motivate us to offer our assistance in this extraordinarily important endeavor. Given the short time frame afforded for comments, we have developed brief bulleted 'talking points', which we believe should lead to more substantive interactions with NAPA stakeholders. We welcome any immediate opportunities to engage in substantive dialog in support of moving from 'act to action' and suggest that we consider a face --to-face meeting at the upcoming ICAD conference.

Talking points

1) Increase the diversity of the stakeholders involved in development and implementation of the Plan. There are many ex-US Alzheimer's initiatives with convergent goals and objectives. Insuring communication and interchange of information (using many of the technologies envisioned in the draft) will improve efficiency and reduce redundancy in action/implementation of steps listed in the Plan. Similarly, the pharmaceutical industry's scientific and clinical leaders in Alzheimer's Disease have a uniquely global view, as well as insights into development pipelines and research methodologies. These channels for shared learning should also improve cost-efficiencies for NAPA implementation.
2) The 10 year plan envisioned for the development and deployment of preventive strategies is ambitious (reminiscent of President Kennedy's challenge for the Apollo program) and implicitly

assumes that one of the treatments currently in the clinic will succeed. There are numerous novel approaches further back in development, which might ultimately be the most successful candidates. ISCTM has hosted a symposium evaluating lessons learned from the gamma-secretase inhibitors and other therapeutic trials, the critical importance of early clinical pharmacology/translational studies, and the use of biomarkers as diagnostic, response, and personalized medicine tools, and is eager to share our appraisal and recommendations for state-of-the-art accelerated drug development strategies.

3) Clinical trials designs for Alzheimer's disease and other neurodegenerative disorders are undergoing re-evaluation, given the tremendous costs and lengthy time frames necessary for the fulfillment of a 'traditional' regulatory path to drug approval. We suggest further exploration of novel strategies to accelerate and improve trials design including:
    a. Stratified enrollment such as 'banding' different ages/stages of illness in a disease course modification/prevention trial including treatment arms for pre-clinical, MCI, mild, and moderate patients.
    b. Selection of high risk volunteers/patients with potential accelerated course to demonstrate proof of concept (familial Alzheimer's disease, or APOE4 genotype)
    c. Interim analyses to satisfy a modified regulatory approval process that incentivizes investment in long-term trials, including provision for study continuation to occur as a post-marketing commitment.
    d. Incorporation of naturalistic designs where all subjects are given the opportunity to remain in the protocol whether or not 'dropped from treatment'.
    e. Other issues to consider:
        i. Development and validation of more sensitive neuropsychological testing
        ii. Use of prodromal /pre-clinical biomarkers, cognitive and/or behavioral symptoms to reliably identify 'at risk' subjects.
        iii. Multi-factorial approaches to risk identification and patient selection. What is the most appropriate patient population (severity and course) for distinctly unique treatments to mitigate or prevent Alzheimer's Disease?
        iv. Develop and validate improved measures to assess long-term treatment effects.
        v. How long should patients be followed?
        vi. Disease progression trials in Alzheimer's Disease might need to be 'targeted' to improve the probabilities of success, and better identify multiple pathological processes, e.g., tau-opathy vs. amyloid burden, or both.

vii. What are the ethical issues involved in treating patients that are asymptomatic?

4) Assessment modalities used currently for staging of illness, i.e., CDR, MMSE, and for 'efficacy' outcomes, i.e., ADAS-COG and ADCS-ADL, are not sufficiently sensitive or validated for use in the pre-clinical and very early Alzheimer's treatment trials. Increased funding to support the development and validation of more sensitive instruments is essential. Increase the use of behavioral/psychiatric assessment tools to determine disease progression given the entwined relationship of the early clinical course (with diagnosis validated by other accepted approaches).
5) Compare and contrast the time course, neurochemistry, clinical presentation, treatment modalities, and assessment strategies, for various dementias characterized as disorders of 'protein folding'. Data sharing, lessons learned, and methodological innovation in one area of research should improve efficiencies in meeting the objectives in the Plan.
6) Address public health policy drivers which can increase the incentives and share risk with pharmaceutical companies and other treatment development consortia, i.e., intellectual property –patent considerations, insurer/provider commitments to utilize treatments, regulatory incentives and development of Guidance in support of Alzheimer's Disease treatment development, and public health education awareness to support screening and participation in clinical trials.

Again, ISCTM thanks the Alzheimer's Association for the opportunity to review this draft document. It is our hope that these comments will be of use in the ongoing discussion and revision of the Plan, and to foster an increased collaboration with ISCTM and its membership and other key stakeholders. Should there be questions about any of our comments, we would be happy to discuss them, and we also hope that we can arrange a meeting during the ICAD meeting to further expand our involvement in this critically important endeavor.

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