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KEY ALZHEIMER'S DRUG DEVELOPMENT STAKEHOLDERS JOIN FORCES TO ESTABLISH CLINICAL TRIAL SAFEGUARDS AND ACCELERATE DISCOVERY

- Unique alliance unites FDA, academic scientists, pharma industry & Alzheimer's Association -

CHICAGO, July 12, 2011 – New recommendations to protect participant safety in clinical trials of certain Alzheimer's disease drugs have been drafted by an expert working group convened by the Alzheimer's Association® through its Research Roundtable and are published online today as [an article in press, ahead of print](#) by *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*. The working group included scientists from academic research centers, the pharmaceutical industry, and the Alzheimer's Association. An [accompanying editorial](#) authored by three working group members explains the rationale behind the recommendations.

These recommendations were presented to the U.S. Food and Drug Administration (FDA) by the Alzheimer's Association Research Roundtable. They have been accepted by the FDA and are already being incorporated into research studies. These safety recommendations address possible side effects of drugs aimed at a toxic protein called beta-amyloid – a prime suspect in the development of Alzheimer's.

The working group designated the side effects “amyloid-related imaging abnormalities” (ARIA). They are changes in the brain that are detected on magnetic resonance images (MRI) of some participants in recent clinical trials of amyloid-lowering drugs.

One key question the working group faced is whether ARIA are temporary symptoms of ongoing Alzheimer's treatment – somewhat analogous to nausea and hair loss from cancer chemotherapy – or evidence that amyloid-lowering therapies may have more serious side-effects.

Current knowledge doesn't provide definitive answers to this critical question. But stakeholders in the Alzheimer's drug development arena – including individuals and families affected by the disease, academic thought leaders, the pharmaceutical industry and the Alzheimer's Association – agree that gaining insight into the potential benefits and risks of amyloid-lowering therapies is among the most pressing questions in Alzheimer's research.

At the same time, protecting trial participant safety is paramount. The ARIA guidelines published online today offer a credible, consensus-based roadmap on how to proceed. They also create a framework for future research in evaluating amyloid-targeting drugs and their potential side effects.

“These safety recommendations and the process that produced them reflect an emerging movement toward openness and collaboration to bring desperately needed new treatment options to the more than 35 million people worldwide living with dementia,” said Maria Carrillo, Ph.D., Alzheimer’s Association Senior Director, Medical and Scientific Affairs, and a co-author of the article and editorial. “The Alzheimer’s Association is proud to have acted as the catalyst in convening this workgroup. We’re grateful for the investment of time by all the scientists involved, industry’s willingness to look beyond the proprietary interests of individual companies, and the FDA’s willingness to listen, and to act.”

“The working group’s timeline was as inspiring as its process,” Carrillo continued. “We’ve gone from concept to consensus to publication in less than one year, reflecting the urgent need to move the field forward. It was in July 2010 during the Alzheimer’s Association International Conference (AAIC) that stakeholders agreed to join the working group under the auspices of the Alzheimer’s Association Research Roundtable. We publish today, and next week, at this year’s Alzheimer’s Association International Conference in Paris, the scientific presentations include several reports on studies applying the new safety criteria.”

While the new recommendations establish rigorous, evidence-based, volunteer protections, they also ease some more stringent restrictions originally proposed by the FDA in 2010 that excluded certain participants from studies of amyloid-lowering drugs.

Some stakeholders found the original FDA guidance, which was shared with clinical trial sponsors just before AAIC 2010, excessively restrictive. They expressed that these restrictions had the potential to (a) stall progress in evaluating this class of investigational drugs, (b) create a barrier to participant access to clinical studies, and (c) limit the applicability of new therapies in real-world community treatment settings outside research centers.

After considering various options, a group of key stakeholders approached the Alzheimer’s Association about addressing key issues in the FDA guidance through an existing consortium for cross-collaboration among industry, academic, nonprofit, and government communities – the Association’s Research Roundtable.

What Are Amyloid-Related Imaging Abnormalities (ARIA)?

Amyloid-related imaging abnormalities (ARIA) are brain changes detected with magnetic resonance imaging (MRI) in some participants during recent clinical trials of amyloid-lowering Alzheimer’s drugs. These drugs are among the most advanced candidates in the search for more effective Alzheimer’s treatments. They target elevated brain levels of a protein called beta-amyloid, which is one of the hallmark brain abnormalities associated with Alzheimer’s.

Amyloid-modifying drugs can influence beta-amyloid levels through a variety of mechanisms. Removing beta-amyloid from the brain can cause side effects (Note: all drugs have side effects). One of these side effects is amyloid-related imaging abnormalities (ARIA). Two types of brain changes are present in ARIA: (1) microhemorrhages and (2) vasogenic edema.

- Brain microhemorrhages are a common age-related condition. They occur even in neurologically healthy individuals, but occur more frequently in Alzheimer’s, and appear to be associated with amyloid accumulation.

- Vasogenic edema is a condition first identified via MRI in clinical trials of bapineuzumab, a monoclonal antibody targeting beta-amyloid, and has now been reported with other amyloid-lowering agents. The exact nature of vasogenic edema is not known. It is believed that vasogenic edema may be related to blood vessels that become “leaky” due to movement of amyloid from plaques into and then out of blood vessel walls.

The clinical significance of microhemorrhages and vasogenic edema in studies of amyloid-modifying drugs for Alzheimer’s disease is not clear, nor is the relationship between the two conditions. It is not clear whether ARIA may occur spontaneously as part of the aging brain’s natural effort to clear beta-amyloid, or whether these abnormalities are a direct consequence of amyloid-modifying treatment.

It is also not yet known whether ARIA affect the clinical course of Alzheimer’s or an individual’s response to treatment. In most trial participants who developed ARIA, the changes caused imaging abnormalities but no detectable symptoms; researchers identified ARIA incidentally during routine MRI monitoring. In some cases, ARIA caused headache, confusion, visual disturbances or sudden changes in mental status, leading to additional MRI assessments that detected the abnormalities. According to a literature review conducted by the working group, ARIA resolved spontaneously in every case except one, which was treated with intravenous steroids.

New ARIA Recommendations Support Progress in Alzheimer’s Clinical Trials

The FDA’s original 2010 guidelines directed clinical trial sponsors to exclude volunteers with more than two existing brain microhemorrhages. The FDA also required increased monitoring of participants for signs of new microhemorrhages or vasogenic edema, and discontinuation of treatment among any volunteers who developed ARIA during their participation.

The Alzheimer’s Association Research Roundtable working group evaluated all publicly available data about imaging-related abnormalities in clinical trials of amyloid-modifying Alzheimer’s drugs, and issued the following recommendations in the journal article published online today:

- Allow volunteers with up to four pre-existing microhemorrhages to enroll in clinical trials of amyloid-modifying agents.
- Allow volunteers who develop microhemorrhages during a trial to continue participating, provided that their MRI findings are not associated with significant worsening of symptoms.
- Consider dose reduction of amyloid-modifying drugs in clinical trial participants who develop ARIA.
- Increase monitoring of study participants in Phase I and early Phase II studies to gain further knowledge about the mechanisms underlying microhemorrhages and vasogenic edema, the relationship between these two conditions, and whether they have an impact on clinical outcomes or response to treatment.
- Continue close monitoring for ARIA in ongoing studies.
- Propose technical acquisition protocols and reading and reporting standards for MRIs used to evaluate and monitor for ARIA.
- Develop animal models in which to evaluate whether amyloid-modifying therapies in fact cause the blood-brain barrier alterations that are believed to be the underlying cause of vasogenic edema.

- Consider combining MRI monitoring with positron-emission tomography (PET) using amyloid-detecting compounds to better elucidate the relationship between ARIA MRI changes and brain amyloid concentrations.
- Conduct longitudinal studies outside drug trials to better understand the spontaneous occurrence of ARIA and their impact on memory and behavior.

The working group believes the recommendations represent the best possible balance between protecting participant safety and supporting acquisition of essential insight into potential risks and benefits of amyloid-modifying treatments.

According to the authors of the *Alzheimer's & Dementia* editorial published online today, "The working group report was sent to the FDA for review and consideration. The FDA subsequently revised and updated the original advice to sponsors in a manner consistent with the report."

About the Alzheimer's Association Research Roundtable

The Alzheimer's Association Research Roundtable is a consortium of scientists from the pharmaceutical, biotechnology, diagnostics, imaging and cognitive testing industries, and senior staff and advisors from the Association. The Roundtable was formed in 2003 to help identify and overcome common barriers to progress in Alzheimer's drug development. Begun with four sponsors, the Research Roundtable now includes more than 20, who benefit from the state-of-the-field scientific presentations, collegial interactions and networking opportunities. Additional attendees include investigators from academia and government organizations such as the U.S. FDA, its European equivalent the European Medicines Agency, and the National Institutes of Health. For more information, visit www.alz.org/research/funding/alzheimers_research_roundtable.asp.

About the Alzheimer's Association

The Alzheimer's Association is the world's leading voluntary health organization in Alzheimer care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit www.alz.org or call 800-272-3900.

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