Experts call for better design of early drug trials for Alzheimer's and related dementias

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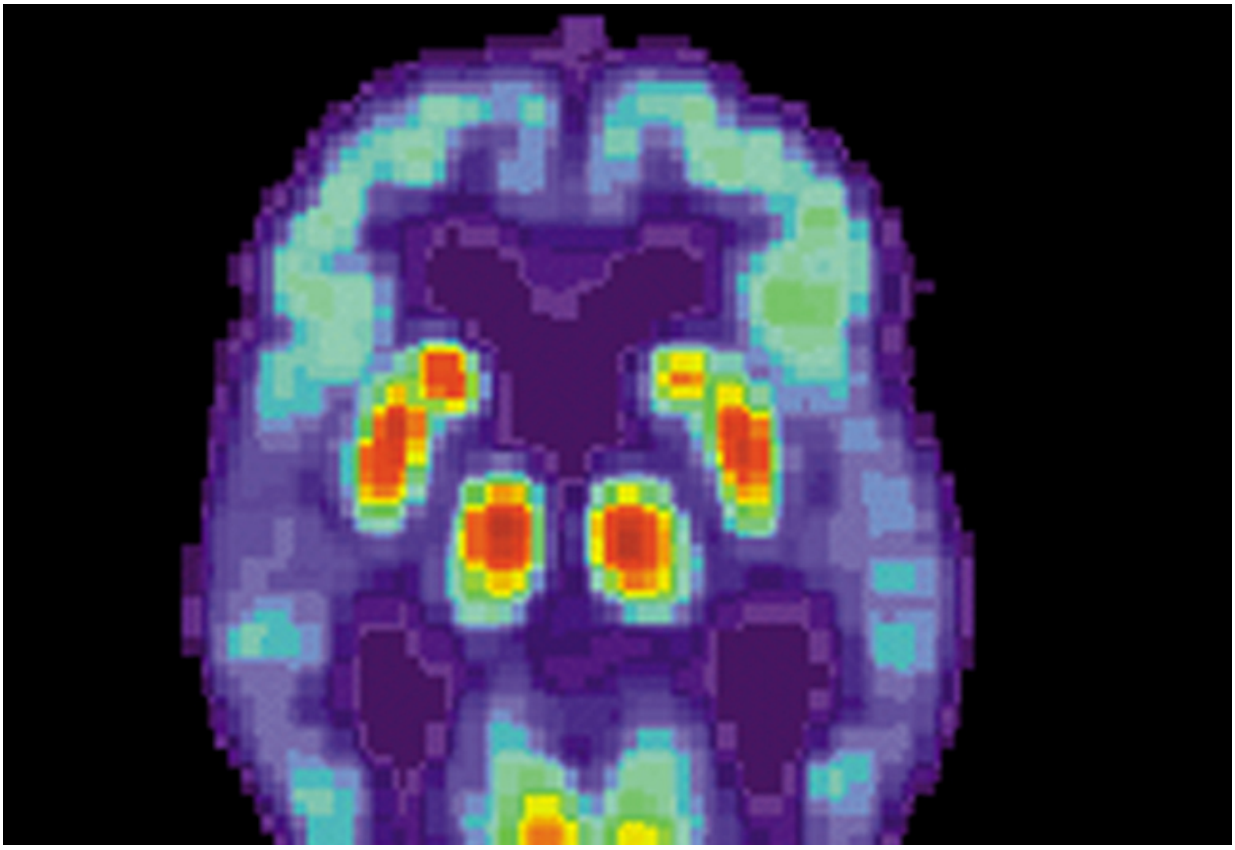

PET scan of a human brain with Alzheimer's disease. Credit: public domain

An expert panel convened by the Alzheimer's Drug Discovery Foundation (ADDF) and The Association for Frontotemporal Degeneration (AFTD) provides guidance on best practices for the design

of early drug trials for Alzheimer's disease, frontotemporal degeneration (FTD), and other neurodegenerative dementias. Their guidance was published in the May 18, 2021 issue of *Neurology*, the medical journal of the American Academy of Neurology.

These efficiencies in clinical trials can help to achieve proof of concept more rapidly and at lower costs. The estimated cost of developing an Alzheimer's drug is eight times more than a cancer drug and takes nearly twice as long to develop. The panel, which comprised clinicians, researchers, and statisticians from academia, biotech, and pharmaceutical companies, as well as ADDF and AFTD scientific staff, focused on early phase 1 and 2 exploratory trials, which assess a drug's safety and pharmacologic effects on patients. Exploratory studies with optimized study designs can terminate programs not likely to succeed and efficiently move promising programs through the clinical trial process. Later phase 2 and phase 3 trials measure clinical outcomes such as memory and ability to perform daily functions.

"The majority of clinical development costs come from later stage phase 2b and phase 3 studies, which require long treatment periods and a large number of patients to detect meaningful changes in cognitive, behavioral, and functional endpoints," said Howard Fillit, M.D., ADDF founding executive director and chief science officer. "Results from exploratory phase 2a trials are the critical inflection point when researchers decide which drugs to move into these larger and more expensive trials, so clearly these phase 2a trials need to be as rigorous and well-designed as possible."

Panel makes four key recommendations for exploratory trial study designs

By adopting best practices in designing exploratory trials, researchers

and companies can be more confident in using their results to make the all-important go/no-go decisions about advancing drugs to larger later-stage trials. The four key panel recommendations are to:

1. Employ rigorous statistical analyses and procedures, engaging statisticians in trial design as early as possible.
2. Incorporate the appropriate biomarker and clinical endpoints that reflect the drug's mechanism of action and the specific study population.
3. Leverage historical data to determine appropriate outcome measures that are well-aligned with the disease and mechanism of action for the treatment.
4. Consider novel clinical development plans to increase efficiency in moving a drug candidate into larger clinical trials or determining that it is ineffective as quickly as possible; avoid "cookie cutter" trial designs that are not optimized or tailored.

"These four recommendations can lead to more efficient trials, with substantial financial savings, as well as more strategic and effective engagement of patients," said AFTD CEO Susan L-J Dickinson. "The latter is a key concern for a rare disease like FTD where the low number of patients pushes the need for strategic study design, with patients enrolled only in studies that will provide a clear and accurate readout of therapeutic efficacy."

"We clearly need exploratory trials to be rigorous and efficient," said Dr. Fillit. "But this is about working toward the ultimate success—effective treatment strategies, which will likely be a combination drug approach that hits several of the biological pathways involved in the neurodegenerative process of dementia. That means being able to take multiple shots on goal—testing a wide variety of plausible drug candidates to identify the most promising ones."

More information: Lauren G. Friedman et al. Value-Generating Exploratory Trials in Neurodegenerative Dementias, *Neurology* (2021). DOI: 10.1212/WNL.0000000000011774