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For Scientists Racing to Cure Alzheimer's, the Math Is Getting Ugly

Vicki Staehr, who lives in Orlando, Fla., has enrolled in a clinical trial for an experimental Alzheimer's treatment intended to slow memory loss. Credit Zack Wittman for The New York Times

By Gina Kolata | July 23, 2018

The task facing Eli Lilly, the giant pharmaceutical company, sounds simple enough: Find 375 people with early Alzheimer's disease for a bold new clinical trial aiming to slow or stop memory loss.

There are 5.4 million Alzheimer's patients in the United States. You'd think it would be easy to find that many participants for a trial like this one.

But it's not. And the problem has enormous implications for treatment of a disease that terrifies older Americans and has strained families in numbers too great to count.

The Global Alzheimer's Platform Foundation, which is helping recruit participants for the Lilly trial, estimates that to begin finding participants, it will have to inform 15,000 to 18,000 people in the right age groups about the effort.

Of these, nearly 2,000 must pass the initial screening to be selected for further tests to see if they qualify.

Just 20 percent will meet the criteria to enroll in Lilly's trial: They must be aged 60 to 89, have mild but progressive memory loss for at least six months, and have two types of brain scans showing Alzheimer's is underway.

Yet an 80 percent screening failure rate is typical for Alzheimer's trials, said John Dwyer, president of the foundation. There is just no good way to quickly diagnose the disease.

The onerous process of locating just 375 patients illustrates a grim truth: finding patients on whom to test new Alzheimer's treatments is becoming an insurmountable obstacle — no matter how promising the trial.

With brain scans, lab tests and memory tests, the cost per diagnosis alone is daunting — as much as $100,000 for each person who ends up enrolled in a trial, Mr. Dwyer said — even before they begin the experimental treatment.

Complicating the problem, the number of trials has exploded in recent years. There are more than 100 Alzheimer's studies looking for a whopping 25,000 participants, Mr. Dwyer said.

To begin filling them all, 37.5 million patients in the right age group would first have to be informed. Ten percent would be referred to a trial site for screening.

Twenty percent of these would drop out, given the current rate, leaving just 150,000 to be screened.

And with an 80 percent screening failure rate, that leaves 25,000 participants of the 37.5 million who were first informed.

The numbers make it clear: There's no way scientists are going to find 25,000 participants for all of the Alzheimer's trials that have been approved.

"The irony is that the science has never been more promising," Mr. Dwyer said. "How many promising drugs will be abandoned or their evaluation seriously delayed? Some good science is going to be left on cutting-room floor."

These trials are not just expensive; so far, they have been expensive failures.

For the most part, researchers have focused on a target that seemed obvious and approachable: a protein, beta amyloid, that starts to accrue in patients' brains years before their memories falter. It is believed to be the first sign of Alzheimer's disease.

For more than a decade, companies tried again and again with anti-amyloid drugs to slow or halt the disease, spending billions of dollars in clinical trials. Lilly alone invested more than $3 billion. Pfizer, after a series of failures, announced in January that it was getting out of the Alzheimer's race altogether.

Yet the need is as urgent as ever. No treatments have yet been found to slow the degenerative brain disease.

Lilly has an advantage: This is a well-known company that can afford a vigorous recruitment effort. It is studying a two-drug combination, the first of its kind.
Even so, recruitment for the trial will be difficult, Mr. Dwyer said: Nine other trials are looking for patients with mild memory loss.

Some seek patients with no Alzheimer's symptoms but who have genetic conditions or biomarkers — like telltale brain proteins — that make it very likely or almost certain they will develop the disease.

Other scientists are seeking people whose Alzheimer's disease is already well underway.

Even worse: Most Alzheimer's patients never think about entering a trial.

There are no successful drugs that might fuel interest. The patients are elderly and simply getting to the trial sites can be difficult. And Alzheimer's patients tend to be seen by private doctors who do not know about or suggest trials.

The stigma of Alzheimer's disease contributes to a natural tendency among patients and family members to deny or hide early signs of memory loss.

"It can take a long time to get a diagnosis," said Dr. Ira Goodman, neuroscience medical director of Bioclinica Research in Orlando, Fla., a site for the Lilly trial. "Even the primary care doctors say, 'Oh, don't worry about it, you're just getting older.'"

Another reason trials might have failed: Alzheimer's diagnoses are wrong more often than is generally realized. So patients who entered trials for Alzheimer's drugs might not have had the disease.

Dr. Goodman and his colleagues studied the brains of 382 patients whose doctors gave them a diagnosis of dementia before death. The autopsies showed that Alzheimer's was not the cause of dementia in 89 of them.

Yet 58 of those 89 patients, or 65 percent, had been incorrectly told that they had Alzheimer's. With a new type of brain scan, rarely used in doctors' offices, an Alzheimer's diagnosis can be more precise.

Daniel Skovronsky, a senior vice president of clinical and product development at Lilly, vigorously pushed for the new trial, arguing that previous studies that failed involved weaker drugs and tested just one drug at a time.

So his plan is to use one experimental drug that stops the poisonous amyloid from being made and another experimental drug that clears away amyloid already produced in the brain.

One-third of patients will get a placebo, one-third will get one of the drugs plus a placebo, and one-third will get both drugs. "Dosing will be high," Dr. Skovronsky said. "The goal is to get rid of 90 percent of existing plaque and block 90 percent of plaque production."

"We know the outcome if we do nothing," Dr. Skovronsky added.

Some experts not involved with the study are optimistic.

"It's a really important experiment and very likely to work," said Dr. Randall Bateman, an Alzheimer's researcher at Washington University School of Medicine in St. Louis.

“This is the cutting edge, combining two drugs,” said Dr. Paul Aisen, an Alzheimer’s researcher at the University of Southern California. “I do think it’s going to work.”

Recruitment began in December. Among the patients who have enrolled is 72-year-old Vicki Staehr, who lives in Orlando, Fla., with her son and daughter-in-law.

“I can’t remember anything for more than a few seconds,” she said in a telephone interview. “If you asked me what I had for lunch today, I couldn’t tell you.”

Her great-grandmother and grandmother had dementia, she said, so she realized a tendency to develop Alzheimer’s might run in her family.

She saw her grandmother decline and knew what the disease does to people. About a year ago, she realized her memory was starting to falter. It was frightening, Ms. Staehr said.

When her neurologist suggested testing to see if she qualified for the Lilly study, she was both surprised and intrigued.

“I’m not sure it would help me,” Mrs. Staehr said “But if it could help someone else. Whether you get it or not, watching it is terrible.”

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