

Questions for the Record

Subcommittee on Health

Hearing Entitled:

"21st Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients."

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Responses from Dr. Samuel E. Gandy

Chair, Alzheimer's Disease Research Center

Mount Sinai Health System

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The Honorable Michael C. Burgess

Question: Would you comment on some of the barriers that Class III medical device manufacturers face when seeking coverage and payment from CMS for innovative and cutting edge technology that improves the lives of patients?

Response: Due to my field of expertise, I can really only speak to neurological conditions and there is little current evidence that would lead one to anticipate the proposal of a Class III medical device for the treatment of Alzheimer's disease. The Class III category is assigned when there is high risk (e.g. neurosurgical implantation of electrodes from which external electrical stimulation [small shocks] can be administered). In neurological and psychiatric diseases in which these devices have proven promising, there is usually some fairly circumscribed brain region that can be targeted with these small shocks. The closest example is in Parkinson's disease, wherein there is a brain region called the subthalamic nucleus that appears to be *overactive*. Now, it might seem counterintuitive to think of stimulating a brain region that is overactive. However, nerve cells constantly alternate between moments of excitation separated by moments of unresponsiveness. The explanation for this is that nerve cells must re-equilibrate after excitation and during this re-equilibration period, they are incapable of being excited. The re-equilibration period permits nerve cells to get ready for the next shock. With just the right timing of shocks from an external source that functions as a sort of pacemaker, nerve cells can be induced to spend more time in those unresponsive, re-equilibration periods. The overactivity caused by the disease is thereby reduced by using shocks to induce nerves to spend more time in the unresponsive state. Alzheimer's disease is different in two ways: (1) there is no obvious area of overactivity; and (2) the brain region involved is massive. The cerebral cortex that is involved in Alzheimer's involves the surface for most of the brain, and therefore is far too large and complex to be managed with shocks, although there are early attempts ongoing. Thus, the major barrier in this instance is really the creation of a Class III medical device that benefits Alzheimer's disease, which at this time seems very unlikely just due to the nature of the disease.

The Honorable Michael C. Burgess

Question: When innovative therapies are FDA approved, there is a significant lag time between FDA approval and Medicare coverage decisions leaving these products to be reviewed and paid on a case by case basis. Many of these initial claims will be adjudicated through the Medicare appeals process. The three year back log at the Office of Medicare Hearings and Appeals for Administrative Law Judge hearings creates a financial disincentive for hospitals and providers to use these therapies given the uncertainty regarding timely reimbursement. Would you explain how this severe backlog would impact your hospital's ability to use cutting edge therapies when the reimbursement landscape for Medicare patients is uncertain?

Response: This OMHA backlog is a tremendous problem, and there is no obvious, “one-size-fits-all” solution. The most recent examples were in the several imaging agents developed for visualizing the type of Alzheimer’s pathology known as amyloid plaque. Small biotechnology firms (e.g., Avid) and major innovators (e.g., GE) developed radioactive chemicals that were successful as amyloid imaging “ligands” (a name applied to an injected chemical that sticks to some partner molecule in the brain). While CMS was evaluating whether or not to reimburse these ligands, the companies donated ligand to any physician who wanted to prescribe their use in diagnosis. The patient was still responsible for the cost of the nuclear medicine department’s time and effort, but the ligand was free. This cut the cost from \$4000 under normal circumstances down to \$1200 during what was called a “voucher” phase (the vouchers were the documents that physicians used to prescribe these cost-discounted scans). In its initial ruling, CMS declined to reimburse for these tests. The companies, hopeful that this is a temporary state of affairs, continue to offer “vouchers” periodically, wherein ligand is available at no charge, in order to keep the professional and advocacy communities engaged. Based on the initial experience with the negative CMS decision for amyloid imaging, some companies (e.g., GE) discontinued their rush to develop competing ligands and instead have taken the strategy of delaying application for regulatory approval for their new ligands and, in the interim, they will partner with certain medical centers. The companies will provide exclusive access to ligands in exchange for having expert faculty characterize their ligands and work out whether the ligands meet some clinical need. In this way, the case for FDA and/or CMS approval will be strengthened and there will be support from the academic community.

In summary, my first draft response at how to improve the CMS appeals backlog would be for the companies to anticipate the backlog and to be prepared to waive costs for some period of time between FDA registration and CMS approval for reimbursement. This would provide the professional community with a trial period during which they would be able to test the new products for themselves. If the products are truly worthwhile, data from the trial period could be used as evidence during the CMS appeal. This is one example for how industry has responded to the evolving landscape of Alzheimer’s diagnosis. In the therapeutic area, pharmaceutical companies have partnered with the NIH for drug testing, especially with the National Institute on Aging’s Alzheimer’s Disease Cooperative Study (ADCS) Group. The ADCS operates as a national CRO (clinical research organization). By partnering with ADCS, trial results are jointly announced, thereby arriving with the imprimatur of an independent federal-academic body. One would predict that this sort of partnership would reduce the need for OMHA, because drugs would arrive with not just a pharma company’s stamp of approval but that of the ADCS (and by

inference, the NIH). Recent partnerships have involved gamma globulin (Gammagard®, Baxter) and solanezumab (Lilly). These examples will not fit all needs arising. More study of CMS applications early in their development is required. In the same way that the FDA encourages pre-IND (investigational new drug) meetings of investigators with the FDA in the trial design phase in order to ensure that the key milestones likely to be required for FDA approval are included in the trial design, perhaps CMS/pharma joint task forces could assess INDs early on in order to identify key milestones likely to be required for CMS approval. While adding an additional review might appear to increase bureaucracy, these “pre-CMS reviews” would almost certainly be less costly less time-consuming than appeals of negative CMS decisions and that would reduce the burden on OMHA. We would encourage any methods that might generate other creative proposals. Perhaps CMS or NIH might hold a national (or international) call for online comment for a 3- to 6-month period so that academics and industry investigators worldwide might contribute ideas on how to solve the OMHA backlog.

The Honorable Cathy McMorris Rodgers

Question: In your testimony, you recommend that Congress develop legislation which provides market exclusivity for orally administered compounds which is independent of their patent life. You put this forward as a solution to one side of the coin-the post-market life of approved therapies. I am certainly open to a discussion on incentives like exclusivity-particularly for therapies where there is a public health need. But I am also curious about what we can do on the other side of the coin the pre-market time period that uses innovation and new science to streamline the approval process and cuts down on the time it takes drugs to get to market. I know you have focused your research on Alzheimer's. Do you have any specific ideas on how we could improve the way we do clinical trials that could help get a breakthrough Alzheimer's drug to market?

Response: First, thank you for your interest in market exclusivity for orally administered compounds for Alzheimer’s disease. Your question contains several parts that I will take in turn. With regard to streamlining the process, additional investment in the FDA is one suggestion that comes to mind. The FDA is one bottleneck in the drug approval process, and that agency is pressed from Congress and from advocacy groups to rapidly approve additional drugs. However, faster approval of new drugs without allocation of the resources that agency would require to accelerate its work will increase the risk that a poisonous or worthless drug makes it to market. Such a rushed approval will cause damage: to patients directly; to the government financially; and to the reputation and reliability of the FDA. Another way to streamline the process might involve wider pre-screening of populations in order to generate groups of subjects for trials. The US Preventive Health Service recently advised against this, since we have no effective drugs, a policy that some investigators see as a “Catch 22”. Even so, accumulation of pre-screened patients is not the most expensive step. Most individuals show signs of Alzheimer’s in their 70s, so if we were able to slow the progress of the disease by 50 percent, most of these individuals would not show symptoms until their 90s. The latest research indicates that our best chance for intervening in Alzheimer’s disease may be at the stage of pre-symptomatic prevention, which means initiating treatment in people in their 50s or 60s. However, prevention trials will be much more expensive than the current treatment trials, which, in turn, are already among the most expensive in

medicine. We now require at least 300 subjects and an 18 month trial to conduct treatment trials that can cost around \$50 million each. Prevention trials, on the other hand, will require screening of thousands of subjects and will last more than five years, potentially costing \$1 Billion in order to move a drug from entry into Phase 1 trials on to the ultimate goal of approval. In order to be approved, a drug must meet certain benefit milestones in at least two independent trials. Given the enormous cost, these trials will be performed serially rather than in parallel. Thus, the newest and most promising innovation in Alzheimer's trials will cause the cost of trials to skyrocket. However, the general consensus is that this is the best next step in terms of research and progression on possible treatments, but the rate of progress will be very slow and very expensive indeed.

The Honorable Cathy McMorris Rodgers

Question: I am aware of ongoing efforts to develop standing Alzheimer's trial sites and robust patient registries as well as efforts to facilitate access to data from unsuccessful trials in a precompetitive manner. What are your thoughts about reforms like these and others? What can we learn from innovative trials in the oncology space to translate into the chronic disease space like Alzheimer's and diabetes?

Response: With regard to standing Alzheimer's trial sites, such a program is maintained by the NIA's Alzheimer's Disease Cooperative Study Group (ADCS), mentioned above in another context. However, the ADCS subject group, in general, already suffer from the symptoms of Alzheimer's disease. Based on what we know about the cause of Alzheimer's and the likely need for presymptomatic intervention, we will indeed require robust registries of people in their 50s and 60s who are willing to commit to long-term prevention trials. Several efforts along this line have been initiated (e.g., the UCSF-Lumosity collaboration on an online brain health registry from which subjects can be recruited for trials). These are low cost strategies for assembling the group of subjects for a trial (called a cohort). However, the expensive part of the trials comes first in the development of the drug and then in reimbursing the physician and staff time and effort involved in periodic assessment. An important part of Alzheimer's clinical trials involves serial neuroimaging studies. The technology here has improved enormously over the past 25 years but the tests cost in the range of \$1000- \$4000 per exam per patient per visit. The administration of the two serial prevention trials required to gain approval for one new drug could cost as much as \$1 Billion. So, while assembling the proper subject cohort is key to running a successful trial, this is by no means the limiting step. The cost of running the trial is limiting.

We agree completely that reports of failed trials should be freely accessible to academic and industry investigators. We certainly cannot afford to make the same mistake over and over. A number of coalitions have been formed wherein major pharmaceutical companies open their shelves to academic medical centers seeking to test drugs that they are not actively pursuing for one reason or another, often because these drugs have failed in some way. In turn, there are major academic efforts at identifying which of these medicines can be repurposed. This is an important collaborative, precompetitive effort. However, as your question implies, we need to know the completely histories of these drugs, including how they have been used in trials and why they have been abandoned.

One key basis for recent successes in oncology has involved a technique known as pharmacogenomics wherein a patient's tumor is studied genetically in order to identify the particular Achilles' heel of that person's tumor. We have had this sort of success at Mount Sinai (<http://www.esquire.com/features/patient-zero-1213>), and we are now applying the lessons learned from cancer to brain diseases such as Alzheimer's (<http://www.mountsinai.org/patient-care/service-areas/neurology/news/nih-grant-to-support-mount-sinai-research-program-to-create-biological-network-model-of-alzheimers-disease-in-partnership-with-new-york-stem-cell-foundation>). A limitation is that in cancer one can usually sample the diseased tissue from a living individual, and this is not practical in brain diseases. However, with the sequencing of the human genome, we can often find subgroups of subjects who respond to drugs, but when the responders are mixed together with the nonresponders, the benefit is diluted out and lost. This means that drugs potentially useful for a responder subgroup will be discarded, often leaving behind no record of the promise that it might have held. An example in Alzheimer's disease can be found in the 1% of subjects in whom we think we know the cause because we have identified powerful genes in certain families. Pharma has typically excluded these subjects out of concern that any successful drug might be labeled as exclusively approved for genetic Alzheimer's disease. The NIA has taken up the cause of these rare forms of Alzheimer's and is co-sponsoring prevention trials known as DIAN (Dominantly Inherited Alzheimer's Network) and API (Alzheimer's Prevention Initiative).

The Honorable Cathy McMorris Rodgers

Question: How can we improve our existing research structure in a way which incentivizes more investment? What is the possibility for clinical trials networks? Or more partnerships with NIH? How about the interaction of the SBIR-STTR program with NIH?

Response: In my testimony, I spoke about the need to create an exclusivity policy for orally administered compounds that can slow Alzheimer's. Most of the drugs that are being studied now are biologics, which means they require refrigeration and administration by infusion. In addition to the challenges of maintaining and delivering biologics beyond university and urban centers, their cost will not bend the dementia care cost curve. In fact, a biologic drug treatment for Alzheimer's could increase the cost of care over 20-fold. If that drug were used to prevent Alzheimer's disease, the cost could increase the current Alzheimer's care expenditure by 50-fold or more.

This extended patent life proposal is aimed at incentivizing the pipeline at all levels. The issue of clinical trial networks was covered in the answer to an earlier question about standing clinical trial sites. Over the past 40 years, the NIH has created a number of nationwide networks of centers aimed at characterizing Alzheimer's patients with clinical and imaging methods and enrolling them into a limited number of trials. This patient network already exists, but there is room for enormous expansion. The trial unit is called the Alzheimer's Disease Cooperative Study Group (ADCS), and they operate only a handful of *treatment* trials in parallel at any one moment. What does not exist are assembled cohorts of subjects in their 50s or 60s who are ready, willing, and qualified to participate in *prevention* trials.

Overall, federal investment in Alzheimer's research is disproportionately meager and needs to be improved. Annual NIH funding for Alzheimer's is around 500 million dollars while that for HIV/AIDS and cancer are in the billions of dollars. The number of affected Americans is far greater for Alzheimer's than for the others. Therefore, the number of dollars invested in Alzheimer's research per American affected is \$85 vs \$2,818 invested in HIV/AIDS research per patient, or \$4,411 invested in cancer research per patient affected. Expanding of the SBIR-STTR program would certainly be welcome and would offset some of the void left by the vacation of venture capital (VC) funding from the Alzheimer's space (as attested during the hearing by the heads of two major VC firms). The SBIR-STTR mechanism can help offset the loss of VC dollars. However, that still would not touch the big ticket item: the cost that we need to offset is the \$1 Billion that we project will cost a drug company to move an Alzheimer's drug from Phase 1 through to approval. As you well know, Congress has stepped in before to provide market incentives for research (i.e., the Orphan Drug Act and the biologics provision in the Affordable Care Act). This created an explosion in orphan drug research. We need an incentive of this magnitude in the Alzheimer's research space.