



Combination Trials Series

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By Gabrielle Strobel

Combination Trials: Time to Open a New Front in AD?

14 February 2013. Over the past year, chatter has been building about combination drug therapy as the "New New Thing" in Alzheimer's disease research. It is not idle talk. In the wake of anemic Phase 2 and 3 results, a movement has sprung up to turn ideas into action. Suggested by none other than **Rusty Katz** of the U.S. Food and Drug Administration, the topic of how the field could pull off clinical trials of two or more unapproved experimental drugs drew some 65 leading scientists and other stakeholders from across the country to Rockville, Maryland, last November. The occasion was the ACT-AD coalition's fifth annual FDA/Alzheimer's Disease Allies Meeting.

The scientists want to develop combination treatments with entirely new science. Rather than combine individually developed drugs in mild to moderate dementia, they are planning to test multiple experimental drugs in the preclinical stage of Alzheimer's. "We are going to have to bite the bullet and be brave, and start combination trials as early as we can do it safely," said **Reisa Sperling** of Brigham and Women's Hospital in Boston, Massachusetts.

Dan Perry and **Cynthia Bens** of ACT-AD, the Washington, D.C.-based umbrella group for Alzheimer's activist groups, hosted the meeting jointly with **Diane Stephenson** of the Critical Path Institute in Tucson, Arizona. C-Path is an applied research organization that engages regulatory with academic, industry, and other scientists to solve pre-competitive drug development problems.

After a day of discussion, the group parted with a pledge to take on the task. It is a large task, in part because testing drugs from more than one company in one trial or preclinical study will require a level of scientific and legal cooperation among companies that is nearly unprecedented in Alzheimer's research. To facilitate such cooperation, the group agreed to whisk away leaders from the FDA, companies, universities, and other stakeholders for a three-day working meeting later this spring, where they would be charged with settling open questions and articulating a coordinated pathway that can be implemented. "Hermetically sealed room," "Manhattan Project," and "The Alamo" were some of the buzzwords that flew around, partly in jest, but partly in recognition of the size of the challenge.

Sperling urged that the spring meeting define specific action items that can be executed with current drugs and biomarkers. For his part, Katz said that the FDA wants to clarify

with researchers exactly how a high-level draft guidance on combination trials that the agency published in 2010 can be applied to specific trial designs in Alzheimer's. **Michael Krams** from Janssen Pharmaceuticals argued for a grander scheme, such as a jointly funded long-term biomarker observational study of up to 30,000 people. This study, "Framingham-on-steroids," as Krams jokingly called it, would develop biomarker fingerprints for each disease stage going back to entirely asymptomatic, and then serve as a platform to spin off "sentinel" patient cohorts into a series of early-stage combination trials. Other speakers pointed to ongoing infrastructure in other indications that already enables multiple companies to jointly test combination therapies, or to contribute discontinued drugs to government repurposing initiatives. While people's individual priorities varied, there was broad agreement that combination trials are both necessary and need a concerted effort to get off the ground. "We want to look back at today and say this is where it started," said Stephenson.

Combination trials per se are nothing new. For years, researchers have tested two individually approved drugs together in one study, or added a single experimental drug to an approved one. For this approach, trial designs are established and the regulatory path is well trodden, said **Owen Fields**, a regulatory strategist at Pfizer. It also has yielded little improvement in Alzheimer's treatment. For new AD drugs, this sequential approach of approving individually and then testing combinations is inadequate, scientists agreed. It is too slow, given that 10,000 baby boomers in the U.S. are turning 65 every day, said **Stephen Salloway** of Butler Hospital in Providence, Rhode Island. Other scientists expressed concern that some new drugs alone do not have robust effects on their own and would be discontinued even though they might well be effective when paired with another drug, especially in early disease stages.

Scientists are hoping to make a dent in the disease by combining two or even more disease-modifying therapies that are themselves in Phase 1 to Phase 3. This has never been done in Alzheimer's research, though it is being done in cancer and being prepared in tuberculosis. And it can work. Last August, the FDA approved a [combination treatment of four HIV drugs](#), two of which were previously approved but two that were new.

Several recent trends have converged to encourage researchers to try their hand at combination trials in Alzheimer's. Setbacks in the clinic have reinforced the idea that it may take attacks on different pathways simultaneously to change the course of a disease as complex as Alzheimer's. Research in tau and inflammation is rising in prominence and bringing these pathways to the fore as drug targets. Genetics research in AD is highlighting cholesterol management, endocytosis, and innate immunity as implicated in AD. "The risk genes tell us it's not one gene, it's not one target, and it's going to take a multiple-target approach to be successful," said Stephenson.

More narrowly, researchers who have conducted anti-amyloid trials say they have learned that hitting multiple targets even within just the amyloid pathway may be necessary to reduce amyloid levels earlier, safer, and more drastically than drugs have done to date. These researchers would start combination testing by adding a BACE inhibitor to an

antibody. That is partly because for this type of combination, several Phase 2 or 3 drugs of both classes exist already.

Regulatory leaders have wanted to see combination trials ever since the FDA started the Critical Path initiative in 2004. Nine years later, both the will and the necessary tools appear to be in place. “We are very eager to develop combinations,” the FDA’s **Bob Temple** told the audience. Both Temple, a senior leader who oversees clinical science at the FDA, and Katz, who directs the agency’s Division of Neurology Products, spoke at this meeting.

The challenges are considerable. Starting with the scientific ones, Sperling noticed that it is unclear how trials can pick up combination drug effects, particularly in early disease stages, where the disease moves slowly. Biomarkers? They are proving their worth for selecting patients and indicating whether a drug hits its intended target. “But in terms of predicting clinical benefit, biomarkers are behind where we hoped they would be,” Sperling said. She was referring to the apparent dissociation between biomarker and clinical responses in the solanezumab and bapineuzumab Phase 3 results (see [ARF related news story](#)).

To Sperling’s mind, this problem can be solved by collecting biomarker information not only from small subsets of trial participants, but also from all participants in several more drug trials, such that scientists have more data to tell how each marker tracks with the subsequent clinical outcome. More sensitive cognitive measures are needed to detect the subtle changes that occur in early AD (see upcoming [ARF Webinar](#) on research in this area).

Getting Started with COMBAT

Gaps in those tools notwithstanding, Sperling has started planning a trial, to be called Combination Therapy in Early AD (COMBAT). The title is intentional. “After all, it is a war, and we are losing,” Sperling said. COMBAT could combine a secretase inhibitor and an immunotherapy to decrease A β production and facilitate clearance. In theory, such a trial could start in a few months, Sperling said. Alternatively, the trial could boost clearance by combining several antibodies that go after soluble, oligomeric, and fibrillar forms of A β . It could combine an anti-A β with an anti-tau drug to try to stem neurodegeneration, or add other neuroprotective or anti-inflammatory agents to any of the above. “I would love to build COMBAT to be a platform where we add COMBAT 2 and 3 as arms when these other drugs become available,” Sperling said.

The trial will contain adaptive features. Alas, which ones? Given the current lack of therapeutic power in the available biomarkers, it is unclear what short-term markers the trial could use to adapt dosing, randomization, or other parameters. One option would be to build early monitoring for ARIA-E into the model, because that side effect is known to happen soon after dosing, if it does. Another option might be to first run a small, continuous CSF monitoring study in some volunteers to determine when CSF biomarkers first respond to the given drugs—hours? days?—and build a lumbar puncture at that time point into the model as a basis on which to adapt. Importantly, the question of what

markers to adapt on could be a deliberate objective of the trial, according to **Don Berry**, a leader in adaptive trial design at the MD Anderson Cancer Center in Houston, Texas. “You build the trial so it will answer that question along with other questions,” said Berry.

FDA Puts Flesh on Bones of Draft Guidance

When the U.S. Food and Drug Administration in 2010 issued a [draft guidance](#) on developing drug combinations, it was written primarily with anti-infectives and cancer drugs in mind. Alzheimer's disease clinicians who have read the guidance consider it too vague to design trials with it. At an ACT-AD/C-Path meeting held in November 2012, **Bob Temple** and **Rusty Katz** of the agency explained it further in a discussion with the audience.

Since the 1970s, companies have had to show that each drug makes a contribution to the claimed effect of a given combination. Dozens of blood pressure-lowering and antibiotic combinations were developed that way. “You have to have reason to believe each component is contributing; otherwise, you are only getting the risk of side effects for no benefit,” Temple said. In recent years, however, scientific progress on underlying disease pathways has loosened this requirement somewhat to where strong biomarkers and pathophysiology knowledge can make the case that each drug contributes. This works best when molecular disease mechanisms are well understood.

For combinations of unapproved drugs, researchers generally have much less safety and dose response information on the single drugs than they do for approved drugs. This complicates testing combinations but should not deter AD researchers, Temple said. If the drugs have added effects in a disease as bad as Alzheimer's, then making combination development as efficient as possible is truly urgent. “It's of potentially enormous value,” Temple said.

Even with little information on the drugs, developing a combination makes sense if there is a compelling biological rationale, for example, if each drug hits a distinct target in the same molecular pathway. If a drug cannot win approval by itself because it only shows an effect in combination, then that is a valid reason as well, Temple said. In breast cancer, trastuzumab, better known as herceptin, falls into this category. By itself it is ineffective, but as a combination drug, it changed breast cancer therapy. Herceptin might not have been found if it were only studied individually. In AD, scientists believe some drugs cannot be developed singly because trials take too long, especially in early stages when the disease worsens slowly and drug effects are subtle. In the absence of strong individual drug effects, a preclinical model could show an additive or synergistic effect of a combination, and a short in-vivo study on biomarkers can establish that the combination is active and has additive benefits, Temple said.

The draft guidance mentions synergy, that is, a greater-than-additive benefit from the combination. That point can be taken with a grain of salt, Temple said. In reality, few established combination therapies in other indications are synergistic. Most are additive. “It is very hard to show synergy. Additive is good enough,” Temple said.

Toxicity and pharmacokinetics would have to be done in the usual ways, plus some research on whether there are drug-drug interactions.

Traditionally, combination trials have shown the contribution of single versus combination therapy with a factorial study. This type of trial design compares the combination with each of the component drugs, all added to standard of care or compared to placebo. One challenge in AD is that blinding such a trial may be tricky if one drug comes in a pill and the other requires infusion.

Factorial designs with adaptive features would be welcome, Temple said. That is, in part, because adaptive trials are well suited to testing several different doses in addition to combinations. Factorial designs can get unwieldy, requiring many arms if the trial starts out with different drugs at different doses. Helping matters, though, is that adaptive trials can drop those arms that underperform on the interim endpoint. This endpoint can be pharmacodynamic. In cancer, some factorial combination trials start out with more than 10 arms, but aggressive interim analysis allows scientists to trim that number within a few weeks or months into the trial.

How well that will work in AD remains to be seen. “The short answer is, if the effect is dramatic, all this works fine. If the effect is small, it’s going to be hard,” Temple said. The great hope is that preclinical and human Phase 1 and Phase 2 do show a contribution by each component. That is because in this situation, Phase 3 could compare only the combination to placebo or standard of care, obviating the need for a factorial Phase 3 that would have to be multiple times as large. “If the effect size is clearly larger for the combination than either of the components, then you have a much smaller Phase 3 study and enormously increased power,” Temple said.

In essence, the news at this point about FDA’s view on combination trials in AD is that the agency intends to be flexible in how sponsors can demonstrate evidence of individual drug contribution. “If a combination does something wonderful, what are we going to do—not approve it because it did not follow all the rules?” Temple said. As an example, he reminisced about his early days as a physician intern. “We’d give people with acute leukemias a drug and [the leukemias] would go away; three months later it was back and they died. Then people developed combinations, and all of a sudden it did not come back. Did we know which drug contributed exactly what? No. You did not need to. You knew the combination made them better.”

A major effect in Alzheimer’s would overcome significant safety problems as well, Temple added.

That said, Katz urged trialists to consult the FDA before going ahead with combination trials. “Everything depends on the details of the drug and the scenario. You have heard me say that before and it’s especially true here. We are very interested in developing combinations,” Katz said, “But there is no precedent. There is no standard case that you could apply the guidance to and be done. You really have to talk to the division.”

Over the past two years, adaptive trials and Bayesian statistics have become a staple of discussions on how to make Alzheimer's clinical trials cheaper and more successful (see [ARF related news story](#)). At the ACT-AD/C-Path meeting, both Temple and Katz encouraged the field to consider such designs and, indeed, some trials are already applying them (see [ARF CTAD story](#)). At the ACT-AD/C-Path conference, researchers brainstormed on how they could launch clinical trials testing several unapproved experimental therapies at once. Adaptive trials guru **Don Berry** of the MD Anderson Cancer Center in Houston, Texas, argued that combination trials in AD should incorporate adaptive features, and that adaptive designs can be used by several otherwise competing companies in a shared infrastructure.

Berry reiterated that more than 300 adaptive trials in cancer at his institution have shown that looking at the data during the trial and adjusting the trial accordingly provides better information with fewer patients and allows a single trial to answer more than one question. On combination treatments, the tendency of tumors to become resistant to a single drug drove innovation toward combination trials as early as the 1980s. A 1993 breast cancer trial answered the question of whether increasing an effective dose of doxorubicin would add benefit (it did not) and whether taxol added benefit over doxorubicin alone (it did). This historic trial used a 3x2 factorial design of three doses of doxorubicin against one dose of taxol or no taxol ([Henderson et al., 2003](#)).

In Alzheimer's trials, endpoints are such a wide open question at this stage that a combination trial could be engineered to address it head on, Berry said. A trial could determine whether drug A affects a different endpoint than does drug B or the combination. It could test whether effects on different short-term biomarkers create synergism toward a benefit on a later clinical endpoint. And it could test if particular patients respond to drug A and patients with perhaps a different biomarker or genetic profile respond to drug B or the combination.

Neil Buckholtz of the National Institute on Aging in Bethesda, Maryland, said that, to his mind, the critical point for succeeding with adaptive combination trials is to first find biomarkers that change, with sufficient measurement precision, in a practicable time frame. He urged that before large factorial studies are undertaken, small studies be done that dispense single drug and combinations over short periods of time and quantify which drug moves which biomarker, and how soon after dosing.

Companies Can Play Well in One Sandbox

In the AD field, most readers can count on one hand the companies that are widely known to have at least two drugs in sufficiently advanced stages to test combinations; Roche and Eli Lilly and Company come to mind, for example. These companies can go ahead on their own with some combination trials, but on a broader scale, single-company trials limit what could be done scientifically. Indeed, at an ACT-AD/C-Path conference held last November in Rockville, Maryland, part of the day was devoted to discussing how multiple companies could be brought to the table for combination trials in AD. Will companies work together on a topic that goes well beyond the accepted notion of

precompetitive space? Their compounds, their clinical trials, and enrolling into those trials rapidly—that is where companies compete intensely, after all.

Will legal concerns trump the scientific rationale? “Based on our experience, the scientists at companies typically say yes, the lawyers may initially say no,” said **Diane Stephenson** of those types of out-of-the-box ideas. Stephenson heads the Coalition Against Major Diseases initiative of the Tucson, Arizona-based C-Path Institute, which co-sponsored the meeting with the Washington-based ACT-AD coalition of Alzheimer’s organizations. Stephenson works toward expanding the accepted definition of precompetitive space to also include a complete understanding of drugs to be used in combination. Intellectual property and data sharing hurdles may seem daunting, but in fact, examples for how to clear them already exist in other indications and even AD itself.

One example in Alzheimer’s research is the Dominantly Inherited Alzheimer Network (DIAN). It developed a legal agreement whereby companies jointly support, with money and expertise, the work necessary to get preclinical treatment trials off the ground, regardless of whether a given company’s drug was chosen. DIAN offered companies a model to join or be left behind. In the end, more than a dozen biopharma companies signed on to this Pharma Consortium (see [ARF related news story](#)), and more have requested entry since then. Drugs by Eli Lilly and Roche went into the [initial trial](#), which started in December 2012. More trials are being planned.

The best-known example in oncology is perhaps the [I-SPY 2](#) adaptive Phase 2 trial platform. It tests the effects of four to five different cancer drugs against a common control on biomarkers that are then correlated with the endpoint. A well-performing drug “graduates” into its own small Phase 3 trial, which the company then conducts on its own while a new drug enters the joint Phase 2 trial. Participating companies sign a unified intellectual property agreement for this arrangement. This was drawn up by the Foundation of the National Institutes of Health, in Bethesda, Maryland, which also holds the IND and interacts with the FDA. I-SPY 2 accommodates drug combinations by embedding them in a factorial design, and drops ineffective arms as Phase 2 proceeds.

“This is essentially an adaptively randomized Phase 2 screening process for multiple drugs,” said I-SPY 2’s co-developer, **Don Berry** of the University of Texas, Houston. “Pfizer, Abbott, Amgen, Merck, Genentech are playing in the same sandbox to participate in it.” Developed originally for breast cancer, this model is being applied as well to colorectal cancer, melanoma, lymphoma, HIV, and other diseases.

For Alzheimer’s combination trials, **Reisa Sperling** of Brigham and Women’s Hospital, Boston, envisioned a consortium that supports a translational mouse core where drug combinations from several companies can be tested simultaneously in multiple model systems. Successful ones would advance into an I-SPY-like system for early human testing. “If a company said I would be willing to test my BACE inhibitor with your antibody on a neutral platform in several mouse strains, then they might come to the table,” Sperling said.

An existing example comes from tuberculosis. The C-Path Institute drives the [Critical Path to TB Drug Regimens](#) (CPTR) initiative to develop new drugs for multidrug-resistant tuberculosis. In 2010, CPTR started with the Bill and Melinda Gates Foundation and the TB Alliance. Its express goal is to develop combination therapy right from the beginning as a way of addressing the worldwide problem of rising multidrug resistance to tuberculosis, said **Debra Hanna** of C-Path. No new tuberculosis drugs were developed for 40 years after the first drugs had come on the market. At present, four old drugs developed individually are given together in a complex regimen that takes up to nine months to clear the infection and causes many people to drop out because the drug-drug interactions make them sick.

CPTR decided to start fresh by developing multi-target combinations of investigational drugs supplied by different companies. The combination is to be developed in parallel, not sequentially, i.e., using unapproved new chemical agents with new mechanisms of action.

The CPTR is a public-private consortium. Its 24-member groups include government, regulatory, advocacy, and other groups, as well as every major company that is developing new TB drugs. Ten working groups advance separate scientific, legal, regulatory, and policy problems in parallel. “We have one very clear but massive mission, which is to accelerate the development of a new, safer, more effective regimen that can be taken for shorter periods of time, by enabling the early testing of combinations,” Hanna said.

Much like C-Path’s CAMD project does for Alzheimer’s, CPTR so far has built drug development tools such as a common CDISC data standard (see [ARF related news story](#)). It is also building a disease model to simulate potential drug combinations that can help companies assess early on if a given combination would likely fail. As does CAMD in Alzheimer’s, CPTR works with international regulatory agencies to push forward the qualification process for tuberculosis biomarkers for use in drug trials.

A critical component of CPTR's work is a legal framework that enables companies to share clinical trial data in a precompetitive environment. This helps them understand better what is going on in their trials, Hanna said.

Yet another example of a successful legal framework for data sharing can be found in the work of the National Center for Advancing Translational Science. NCATS started up in December 2011 after initial controversy around the appropriate role of the NIH in translational biomedical research. **John McKew** of NCATS cited drug repurposing programs to fund the search for new uses for drugs that were proven safe but were then axed because they failed efficacy in their intended indication. In one program, NCATS persuaded eight companies to contribute such molecules, for a total of 58. The companies include some that are active in Alzheimer’s as well, such as Lilly, Janssen Pharmaceuticals, and Pfizer. This program is different from the kind of precompetitive cooperation needed for AD combination trials in that the molecules are ones the

companies are no longer intending to develop. All the same, certain aspects are relevant to the challenge of multi-company Alzheimer's combination trials.

One lies in McKew's experience building the cooperation. "It was very challenging to get the first couple of companies to sign on. Once we had that, it dominoed, and when we closed the process we had companies waiting at the door," McKew said. A similar dynamic occurred during the building of DIAN's Pharma Consortium. Negotiating a model agreement that these first few companies could sign was the most time-consuming component of setting up the repurposing program, McKew said. It was worth the effort because it pre-empted the need to renegotiate intellectual property and other issues with subsequent companies. NCATS' template agreements for collaborative research and confidential disclosure are [freely available online](#). In discussion, **Rusty Katz** of the FDA noted that the agency encourages such agreements.