“The way these studies are structured to allow for new interventions to be quickly added to the existing infrastructure while they’re up and running fascinates me. It really allows for a perpetual learning opportunity.”
—Jennifer Vates, Project Manager, Critical Care Medicine

“Our typical way of testing drugs is to build this huge, beautiful stadium, test the drug, and then tear the stadium down—and then submit for new funding, build a whole new stadium one block down the road, and test another drug. What the platform does is it establishes the ‘stadium,’ and then you’re just playing different games.”
—Christopher Seymour, Associate Professor, Emergency Medicine

“Ninety-nine percent of patients that we’re treating, we don’t learn anything from them. So the idea that every patient that comes in becomes part of the learning system is an incredible advance.”
—Scott Berry, President and Senior Statistical Scientist, Berry Consultants
In March 2009, two California schoolchildren came down with a cough and fever. Within weeks, the Centers for Disease Control and Prevention had pinpointed their symptoms to a brand-new swine flu. Both children recovered, but their illnesses heralded the global H1N1 pandemic, which killed an estimated 284,000.

After the pandemic, the University of Pittsburgh’s Derek Angus, Distinguished Professor and Mitchell P. Fink Professor, Critical Care Medicine, recalls soul-searching and lament among clinician-researchers who hadn’t been able to respond fast enough. “Here in Pittsburgh, for several weeks, we were inundated with terribly ill H1N1 patients; and yet by the time we got [a] trial up and running, the epidemic was over,” Angus says. Virologists around the world isolated the organism very rapidly, he points out. “[But] we couldn’t even answer the simplest clinical question.”

There had to be a better way—a way to efficiently, affordably learn what every patient has to teach, then to apply those lessons faster. Sepsis, cancer, and other daunting diseases also demand answers faster than traditional trials can provide them.

Angus and his colleagues started thinking about how to fuse randomized clinical trials with clinical practice. Within five years, Angus published a landmark paper in the Journal of the American Medical Association proposing a new approach to clinical trials. The approach is a novel combination of a few forward-looking methods that had met with success in other trials.
The old way of structuring trials is like building a sports stadium, playing one game, then dismantling it. Angus’s team proposed a permanent stadium, a platform ready for game after game. Not only that, it would be embedded in the electronic health record, make incremental changes as it gathers information, and be ready to ask and answer new clinical questions on short notice. It would piggyback unobtrusively on clinical care: UPMC clinicians would invite patients as appropriate; trial organizers would let the system automatically capture blood pressure, adverse events, etc. without having to deploy the usual army of research coordinators and staff. The platform creates what Angus calls a learning health care system.

This April, almost exactly 10 years after the H1N1 epidemic began, Pitt began enrolling patients in one of the world’s first trials that combines the electronic health record with a new, efficient, safety-focused randomization process. The system is powered by software created by the Texas-based Berry Consultants. The approach, called REMAP (randomized, embedded, multifactorial, adaptive platform), may transform the way doctors learn from patients—and how they care for them.
TRY, TRY AGAIN

What’s shown here is a simplistic interpretation of how the first trial using the new REMAP method works. That trial, called SPRY, will determine whether the antidiabetic drug metformin helps older adults recover from surgery. (Sounds pretty neat, eh? Read more about the premise behind SPRY on p. 32.) SPRY is funded by UPMC’s Immune Transplant and Therapy Center. It costs about $5 million, a fraction of what it would cost to run a more conventional trial to answer the same questions.

What we don’t show here is the gold standard for testing therapies—the typical double-blind (where organizers don’t know who is assigned to the placebo or the study treatment), randomized trial. It’s been a hugely important cornerstone in evidence-based medicine. That said, in those trials, researchers usually don’t know which therapy is better until the end of the trial. And the odds of being assigned to it are the same for all participants—50 percent of patients end up with the study drug, 50 percent go on a placebo. Then after the preset time passes, usually years, trial organizers have their results.

In the end, all experimental treatments either get a nod of approval from the FDA or they don’t. REMAP intends to up the odds of happy endings.

NEW

CURRENT

BIOSAMPLES

FUTURE

Pitt’s Derek Angus imagines that REMAP-type trials may one day become part of everyday care. Experimental treatments for cancer, sepsis, and other highly complex problems are particularly well-suited to this approach.

“In a way, it would seem intolerable to ever let your bedside clinician with imperfect knowledge try to make a decision under uncertainty when an overarching adaptive platform may have more knowledge about the best odds of treatment than anything else,” Angus says.
Surgery is hard on the body, which ramps up inflammation as a response to the stresses of the operation and anesthesia. This can lead to postsurgical complications. Inflammation also underlies many aging processes, and high-risk surgery in frail individuals is a little like the aging process. So a therapy that boosts resiliency after surgery might, by the same token, promote healthier aging, too. The Strategies to Promote Resiliency (SPRY) clinical trial—Pitt’s first in the overarching REMAP platform—is testing whether the commonplace diabetes-control drug metformin might be such a therapy. Metformin intrigues anti-aging researchers because it has a wide range of beneficial effects, including reducing inflammation and extending life span in other organisms. If it reduces complications in postsurgical patients over a few months, it might slow aging, too.

And metformin is just one of many possible therapies the research team can test. Even non-drug interventions like physical rehab before the operation could be added as treatment arms.

“That's the concept behind SPRY—to create a platform where we would allow patients, should they consent, to be randomized to different strategies that are almost like anti-aging strategies,” Pitt’s Derek Angus says.

Using the new trial design, principal investigator Matthew Neal, Pitt’s Roberta G. Simmons Assistant Professor of Surgery, says, “we can study drugs like metformin in a leaner, more efficient way, so that every new exciting drug that has the potential for prehabilitation, or has the potential to be an anti-aging strategy, is not sidelined by the burden of eight-digit trial budgets, which would make it prohibitive.”