In ancient times, medical advances were made through a mixture of experimentation, observation, trial and error.

By those standards, clinical trials have been going on for thousands of years.
But today’s trials, heavily regulated by the Food and Drug Administration, are a far cry from the methods of discovery made by early civilizations. Now, long before humans become involved, there are decades spent in laboratories across the world, basic scientists poring over data sets, seeking answers, creating hypotheses. Theories are tested on cell cultures, then fruit flies. Small animal studies then follow.

Theories are strengthened. Some are disproven.

A few make it through to clinical trials.

This is where the path to healing begins.

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Mona Lisa Mejia’s life changed in April 2015. She began having severe headaches—what she believed were bad migraines. There was crushing pain. Nausea. Weakness.

What was believed to be a sinus infection was eventually diagnosed as Stage 4 non-small cell lung cancer that had spread to her brain.

Her case was somewhat unique. While non-small cell lung cancer is the leading cause of cancer-related deaths worldwide, about 15 percent of patients also have a genetic mutation of a critical protein. That protein, called epidermal growth factor receptor, lies on the surface of cells and causes normal cells to grow and divide. In these rare cases, too much of the protein fuels rapid growth of tumors throughout the body.
She immediately began radiation therapy to shrink her brain tumors. For her lung cancer, she turned to a clinical trial.

**Life-changing results**

The university has offered clinical trials almost since the day it opened in 1968. Clinical trials are research studies that depend on human volunteers to explore whether a medical strategy, treatment or device is safe and effective for humans.

Clinical trials may involve treatments under development by pharmaceutical or biotechnology companies, or by independent researchers. Some test new therapies, while other trials test new combinations of already available treatments.

“At any one time at [UT Health San Antonio], we have about 1,500 research studies that involve humans,” said Joseph Schmelz, Ph.D., assistant vice president for research administration. Not all of these research studies end up in clinical trials, however. Many depend on human volunteers simply for observation.

“If we drill down, probably half of those are clinical trials where we are actually testing and looking for ways to deliver health care,” he said.

On average, about 160 new clinical trials are started here each year. Studies can range from endodontics and respiratory care to diabetes treatments and cancer therapies. The majority are cancer trials, mirroring the national average of about 30-40 percent of all trials.
“As an academic health institution, we have faculty who are doing research in all areas. You’re not going to get that anywhere else in San Antonio,” Dr. Schmelz said. “There are plenty of great physicians in the city, but what is unique about [UT Health San Antonio] is that it’s where clinicians and scientists and physician scientists come together and collaborate. That’s what it takes to do science.”

And that science can have life-changing results.

In 2013, a study on finasteride, a drug used to treat enlarged prostate and male pattern baldness, was called one of the most significant practice-changing discoveries of the year. It took researchers from the Cancer Therapy & Research Center (CTRC) more than a decade to conduct the first trial, then they continued with dozens more that followed 19,000 men over many more years. The result: a new prevention drug for prostate cancer that reduces a man’s risk of prostate cancer by almost a third.

Around the same time, the first clinical study to prove that children’s oral stem cells could regenerate their teeth was conducted by researchers in the School of Dentistry. The discovery led to the definition of a new term in the field: regenerative endodontics, and a new treatment offering for children facing the prospect of total tooth loss or a root canal.

And just last year, a CTRC patient became the first person to have radioactive nanoparticles inserted by a catheter into a tumor of the deadliest form of brain cancer, glioblastoma, which kills two-thirds of patients within five years. The experimental gene therapy was found to
nearly double the overall survival of patients with a recurrence of the cancer.

Breakthrough studies are continuously underway: The first pharmaceutical intervention shown to extend the lifespan of middle-aged mice, rapamycin, was first proposed by university researchers as an intervention for aging and has been used in cell and animal studies ever since. The first human clinical trial began in 2013 and is ongoing.

“You think of the investment that goes into the science that it takes to create that kind of treatment, it’s almost immeasurable,” Dr. Schmelz said. “You think of all the postdocs and all the people that work in those labs and all the experiments they do over sometimes 25 or more years, to get to this point and build upon those ideas, it’s all to improve health care.”
Right now, researchers are trying to regrow salivary gland cells in a micro-environment in the hopes that someday they can transfer them into patients.

Once salivary glands are damaged, the effects are permanent. Tissue engineering could help millions in the U.S. with dry mouth due to Sjögren’s syndrome, as well as radiation for head and neck cancer.

Searching for help

Mona Lisa Mejia’s diagnosis of non-small cell lung cancer was a blow to her family. They were still recovering from the death of her 18-month-old daughter to sarcoma, a rare cancer that grows in the body’s connective tissue. And with the double whammy of the genetic mutation in her own body, Mejia’s treatment options required a unique solution.

Her doctors turned to a clinical trial to compare two treatments for the specific type of cancer she has.
She began treatment June 1, 2015, receiving afatinib, an oral medication. Another group of patients received intravenously a combination of that drug and cetuximab, a common chemotherapy treatment.

Through the trial, researchers are trying to determine which treatment option is the best. Animal studies showed a combination of the drugs worked better than either one alone.

This June, a year after her first treatment, Mejia was given good news: her tumors have shrunk and are stable.
Right now, scientists are using fruit flies to explore ways to prevent the earliest triggers of Alzheimer’s disease.

Fruit flies affected by Alzheimer’s have tunnel-like features in the lamin, a mesh-like skeleton that protects brain cells’ control center. This shows lamin dysfunction can cause the death of brain cells, something that appears to be specific to Alzheimer’s.

A complicated process

Before a new treatment can be tested in people, it must first go through a rigorous discovery process in research labs. Possible side effects are evaluated through small animal testing, carefully regulated by the university’s Institutional Animal Care and Use Committee to ensure the research is performed in an ethical and humane manner. If there is success in animals, the next step is often human clinical trials. Before getting approval to move on to clinical trials, investigators must write detailed plans on why they are conducting the study and how it will be administered. What are they trying to prove? What is their primary end point? What is the time frame? How will data be gathered?

Everything is carefully documented. Federal guidelines must be followed to the letter.

It takes very little for this process to get tangled up, and for researchers to have to begin again. Some have to entirely scrap their projects.
“It’s really complicated,” said Bob Clark, M.D., MACP, assistant vice president for clinical research. “There are so many things that have to happen along the way, and they have to happen right and they are mostly in serial array so that if this one over here gets messed up, you don’t get to these other ones until much later, maybe.”

Then the proposal must go through the university’s Institutional Review Board, which evaluates whether the study is ethical and volunteers are adequately protected.

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“The closer they get to humans and the closer human research gets to clinical trials, the more regulations and oversight is placed upon the research,” Dr. Schmelz said. “It’s a burden in that it is additional work and effort, but it has to be done.”

Many proposals never clear this stage. Nationally, only one out of every 1,000 drug compounds in preclinical testing is promising enough to continue to the investigational new drug application process, according to the Department of Health and Human Services.

For those that do, they may face another decade or longer in clinical trials.
Right now, scientists are searching for the root cause of Parkinson’s disease so that someday there will be a treatment.

Small animals afflicted with the disease are revealing a timeline of decline as the disease kills dopamine neurons, leading to debilitating movement deficits. Scientists hope understanding the disease’s progression could lead to a drug that will stop it and lengthen time patients have to lead healthy, productive lives.
Ancient medicine that depended on observation and anecdotal evidence of successes and failures led to some key advancements in health care. Advancements in technology, data gathering and documentation, and lessons learned from global drug disasters led to the creation of the controlled and extensive therapeutic trials of today.

“You can’t even do a clinical trial until the FDA has blessed it,” Dr. Clark said. “There’s an additional level of assurance for volunteers that it is a legitimate and safe thing to do.”

Today’s clinical trials program is divided into phases, with phase 1 being the first time a new drug or device will be tried in a small number of people. It screens for safety, dosage ranges and side effects. Phase 2 includes a larger number of volunteers and tests effectiveness and safety. Phase 3, which involves several hundred to several thousand patients, confirms effectiveness and compares the investigational therapy to standard treatments already in use. Side effects are monitored and information collected to ensure the treatment will be used safely.

A treatment will only pass through to the next phase if it has been found safe and effective.

Phase 3 is typically the final phase before the therapy becomes available in the marketplace. Occasionally, a trial will enter phase 4, but this is largely reserved for therapies already approved by the FDA and being proposed for a new use.

“It is with this idea of rigorously testing ways that deliver health care in a scientific manner that we have the ability to decide whether the changes
that we want to make really do result in improvements in health care,” Dr. Schmelz said. “Clinical trials are very much this idea of experimentation and controlling all of the variables and testing hypotheses.”

The rigor comes at a hefty price: Before a drug clears all phases to make it on the pharmacy shelf, the Department of Health and Human Services reports, it will cost anywhere from $44 million to more than $115 million. Dr. Clark said the reality is much higher—with scholarly articles estimating the cost at around $1 billion per drug.

“It is extremely expensive,” Dr. Schmelz said. Studies that originate with university investigators start out small, but as a therapy shows promise, it must be tested at multiple sites.

“Eventually they have to expand to multicenter clinical trials,” Dr. Schmelz said. “So that means you are going to have to migrate the research to other institutions and you are going to have to get other people at those institutions to run the trial for you. And in order to do that, it takes quite a bit of infrastructure.”

Funding comes from the federal government, private industry, medical institutions and foundations.

**Finding participants**

Even with the creation of online clinical trial databases that pair volunteers with investigators, many trials struggle to get enough participants for a legitimate study. Only about 3 percent of cancer
patients enter clinical trials, according to the National Cancer Institute, and the reasons range from fear of a reduced quality of life to the inconvenience of participation. Nearly half of all cancer clinical trials nationally fail to enroll enough patients and can’t be completed.

Mona Lisa Mejia viewed her participation in her clinical trial with hope, even as she struggled with side effects from her cancer treatment. At the beginning, diarrhea and fatigue were constant battles until her body adjusted to the medication.

But being in the trial gave her purpose.

“My kids are worried about me, but we continue to have faith in God,” she said. “Our faith has gotten us through all of this and without it I would have lost hope. I prayed and he answered. He sent all of these angels to help me. I am just so grateful.”

For health or science?

Not every clinical trial works the way the researchers hypothesize. Patients for whom standard therapies don’t work hope for a miracle cure. Yet some may get no benefit.

If there is a benefit, but the study hasn’t yet cleared phase 3 and received FDA approval, the therapy will no longer be available for participants once their trial is complete. And there is never a guarantee that the FDA will approve the new therapy for use in people.
“We have an extensive informed consent process where we try to make all participants understand the limitations of their own personal benefit,” Dr. Schmelz said. “Really, the benefit is to the knowledge we will gain in the future, and I think most people are willing to give of their time and effort to help in science.”

Many participants realize that greater benefit when they enroll, Dr. Clark said.

“Partly they are hoping they might get some personal benefit, but I think many of them have a very broad perspective on it and a sense that it is something they’re doing for societal benefits,” he said. “They want to make a contribution.

“The trial may not cure whatever it is they have, but because of their involvement, physician scientists will learn something that will help future generations of people.”

**STEP 4**

Right now, people of all ages are participating in clinical trials in the hopes of finding new therapies to eradicate the world’s deadliest diseases.
At any one time, the university has 1,500 ongoing research studies that involve humans. About 160 clinical trials are begun each year and can range from endodontics and respiratory care to diabetes treatments and cancer therapies.