Trials and tribulations

Clinical trials and the road to new arthritis medicines

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When flying instructor, Anne Dooley of Saskatoon, Canada, experienced pain and inflammation in her joints, she visited her family doctor. His reaction was not what she expected.

"He barely glanced at my painful joints, and just told me that I should expect aches and pains as I grew older."

Dooley had a family history of arthritis and decided to seek the opinion of another doctor. "When I sought a second opinion, I was diagnosed with rheumatoid arthritis and promptly referred to a rheumatologist. Had I believed that first doctor I have no doubt that I would now be severely disabled."

Dooley's initial treatment required taking non-steroidal anti-inflammatory drugs (NSAIDs) to reduce the inflammation in her joints and provide pain relief. This group of drugs, which includes aspirin and ibuprofen, are relatively effective but often lead to unwanted side-effects including stomach upsets and gastro-intestinal bleeding. Unfortunately for Dooley she suffered side-effects which she discussed with her rheumatologist. He offered her the opportunity to participate in a clinical trial to investigate a drug that researchers hoped would be as effective as her existing treatment but minimize any side-effects. It belonged to a class of drug known as cyclo-oxygenase (COX)-2 selective inhibitors. COX-2 is a naturally occurring enzyme associated with pain and inflammation. Dooley met the recruitment criteria for study enrollment, but despite her crippling pain she was not convinced.

"At first I thought, does he think I'm crazy? Why would I take a drug that hasn't been tested and approved? I'm not looking for a drug to take for a day, a month or a year. I need a treatment that will be safe for me to take for the rest of my life!"

After several days crippled with pain, Dooley realized that while there were risks associated with this new treatment, the drug also offered hope. She said a wave of altruism swept over her. "If this drug works for me, it could work for others and if it doesn't work, we need to know."

After careful consideration of the pros and cons of participating in a

Definitions

A **clinical trial** is a research study in human volunteers to answer specific health questions. Clinical trials are conducted in phases. Each phase has a different purpose and helps answer specific questions.

Informed consent is the agreement to participate in a clinical trial. It is made voluntarily after being informed of all potential risks and benefits associated with the study.

Every clinical trial begins with a **study protocol**. This document describes the objective(s), design, methodology, statistical considerations and organization of the trial.

A **sponsor** is a person or entity that initiates, funds, or is responsible for a clinical research study.

A **serious adverse event (SAE)** is any event that results in death, life-threatening situation, hospitalization, persistent or significant disability/incapacity or a congenital anomaly/birth defect or requires medical intervention to prevent one of the outcomes listed above.

Source: *The Guardian newspaper,* UK

FOCUS ON
CLINICAL TRIALS

Patients increasingly want to be involved with cutting-edge research and to participate in clinical development. An estimated 1 million Americans each year are willing to put the potential rewards from enrolling in a clinical trial ahead of the possible risks.

Anne Dooley enrolled in a clinical trial of a new arthritis drug. Although initially sceptical, her experience was a great success and her condition was markedly improved.

clinical trial, Dooley signed an Informed Consent Form and was accepted on to the trial. Her experience was a success story: the investigational drug effectively treated her symptoms, she experienced fewer side effects than with her previous medication and the drug was eventually approved for use for arthritis sufferers worldwide.

From test-tube to pharmacy shelves

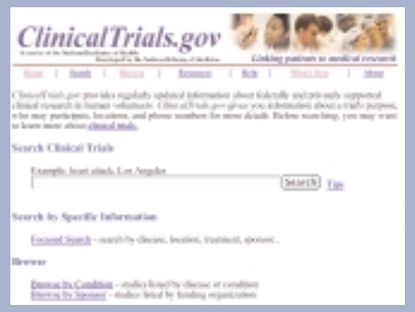
With 170 types of arthritis currently identified and over 70 million sufferers in the U.S. alone, it would be unrealistic to think that one drug, or one class of drug, would be appropriate to treat all arthritis patients. The chronic nature of the illness necessitates close monitoring of any long-term drug-related side effects, and the flexibility to alter drug dosage and type.

Dooley's participation in a clinical trial formed one small but vital step in a complex system that has evolved for taking a researcher's idea in a laboratory to a safe and effective marketed product. Results from clinical trials comprise the single most important factor in determining whether a drug will be approved for commercial use in humans. Even after a product is approved, further clinical studies are conducted to determine the long-term safety and efficacy in the real world setting.

A long and costly process

Conducting a trial is a long and costly process. On average, it takes 15.3 years for an idea in the laboratory to reach the pharmacy shelves, and only 1 out of 5,000 potential compounds will make it. In the U.S. alone, the annual cost of clinical trials is $7 billion, with the estimated cost of patient recruitment alone at $1.89 billion.

The burden of cost usually lies with pharmaceutical or biotechnology companies although sponsorship may be provided by medical institutions, voluntary groups, non-profit organizations, or federal agencies. In the U.S., the two largest sources of research funding for arthritis research are the National Institute for Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and The Arthritis Foundation. In fiscal year 1999, NIAMS spent more than $111 million on arthritis research, and The Arthritis Foundation contributed more than $21 million.



The Internet has had a dramatic effect on both clinical trial management, and patient recruitment.

Good Clinical Practice – protecting patients

With such costly stakes, it is perhaps not surprising that there are many ethical considerations surrounding clinical trial design and conduct. Concerns are sometimes voiced that because of the vast amounts of money pharmaceutical companies are investing into a trial there could be conflict of interest.

To counter this, an elaborate system of protection mechanisms has been established to protect all patients participating in clinical studies. At the core of this system are globally applicable standards for trial conduct known as Good Clinical Practice (GCP) guidelines. If clinical trial data is to be acceptable to regulatory authorities such as the U.S. Food and Drug Administration (FDA), the Japanese Ministry for Health and Welfare (MHW), and the U.K. Medicines and Healthcare products Regulatory Agency (MHRA) it must comply with GCP. These agencies may perform on-site inspections and data audits at clinical trial facilities to ensure that appropriate standards are followed. Under GCP regulations, an Institutional Review Board (IRB) is charged with ensuring that all clinical trials are conducted safely and ethically. IRBs are committees of physicians and scientists assembled by the pharmaceutical company, university or other sponsor conducting the research. The IRB can halt trials if protocols are not followed or if significant adverse reactions occur.

Cutting-edge research

Despite the safety net that has been established to protect participants, clinical trials are a risky business. CenterWatch, a Boston-based publishing company that concentrates on the clinical trial industry, estimates that one out of 30 participants will experience a serious adverse event during the course of a clinical trial.

Despite these risks, a survey by the journal *Arthritis Today* has shown that new research is the subject that most of its readers want to know more about. Patients increasingly want to be involved with cutting-edge research and to participate in clinical development. An estimated 1 million Americans each year are willing to put the potential rewards from enrolling in a clinical trial ahead of the possible risks.

The reasons for participation are varied and complex. For many, there is an

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Dan McDonald

element of desperation. If existing drugs are not controlling their pain and inflammation, they may welcome the opportunity to try a medication that is not yet available to the public. There are also practical considerations: clinical trials offer patients access to study-related physical examinations, regular medical testing, and free investigational medications.

Others, particularly in the advanced stages of their arthritis, are interested in assisting in the advancement of drug development in order to help discover a future treatment, as noted by Professor Richard Day, Professor of Clinical Pharmacology at Sydney's St Vincent's Hospital. "There is a lot of altruism of citizens getting involved in trials - we need to really respect that with complete transparency about trials."

Access to information

Traditionally, arthritis patients received information concerning clinical trials almost exclusively from medical specialists in university hospitals. This system had its drawbacks, causing recruitment delays and some patients to feel excluded from participation.

Recently, more primary care physicians are becoming involved in clinical trials, increasing patient access to studies. Patients are also actively seeking clinical trial information, wanting to be more empowered to make treatment choices. Not-for-profit organizations such as The Arthritis Society are helping to educate arthritis sufferers about the importance of clinical research, and showing them how they might participate in clinical trials. In one initiative, The Arthritis Foundation is working with the National Institutes of Health (NIH) and the National Library of Medicine to develop a database to facilitate patient access to all clinical trials within the NIH system and provide the opportunity for study enrollment. The Internet has also had a dramatic effect on both clinical trial management, and patient recruitment. Companies now offer a variety of services designed to facilitate both patient and investigator access to clinical trial information. CenterWatch currently posts 35,000 clinical trials on its website. Of the 850 rheumatology trials listed, 51 are arthritis trials and approximately another 100 are classified as osteoarthritis trials. Traffic to the site has risen dramatically, from 1.3 million page views in March 2000 to 3.9 million in March 2003.

"The internet is a convenient and in many cases private way for patients to access a variety of in-depth health resources from the comfort of their homes 24 hours a day, 7 days a week," says Dan McDonald, Director of Internet Services at CenterWatch. "Therefore, patients are empowered and able to develop domain knowledge of their condition and are better equipped to make decisions about their health, along with help from their primary care physician."

An explosion of treatment options

Since Anne Dooley was first diagnosed with arthritis there has been an explosion of new treatment options for several types of arthritis. These include new COX-2 selective inhibitors and DMARDs (disease-modifying anti-rheumatic drugs) such as tumor necrosis factor medications and the medical community is hopeful for the future.

"Look out for more biologics targeting identified pathophysiology of patients with various forms of arthritis," says Professor Day. "There will be more precise individualization of therapy based on individual patient characteristics and their disease mechanisms and features. Gene therapy and stem-cell based technologies are coming along with more focused delivery of medicines to sites of action with less exposure of the rest of the body to unneeded medicines. Device drug combinations will become more common and nanotechnology will assist with delivery of potent medicines to precisely identified locations. We will also figure out how to make these drugs more widely available across the global village without slowing the pace of discovery and development of needed pharmacotherapeutic advances."

These advances will only become reality with the continued participation of people with arthritis in well-designed clinical trials. In Dooley's words, "Arthritis must be visible and the problems made plain. The stakes are high. Arthritis sufferers have children and grandchildren at risk from the disease. I don't want arthritis to shatter their dreams."

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TARGET – a global approach

Arthritis is a global problem. Osteoarthritis alone accounts for half of all chronic conditions in those age 65 or over. To expedite the process of making a new drug available to patients worldwide, clinical trials are being designed to test new products in a global setting. Currently, the largest ever worldwide arthritis trial is underway in more than 800 sites throughout the United States, Europe, South America, Canada, South Africa and Asia. The trial known as TARGET (Therapeutic Arthritis Research & Gastrointestinal Event Trial) will study more than 18,000 patients over a 52-week period. TARGET will investigate the gastrointestinal and cardiovascular safety of a COX-2 selective inhibitor compared to two NSAIDs.