

# A Focus on Single-Patient Clinical Trials:

## Trials Optimizing Patient Therapy Help Test Drugs with Fewer Patients

A clinical trial comparing a drug and a placebo in two patient populations is an imperfect indicator of whether any given individual will benefit from a new medicine. When responses to an approved drug vary widely, doctors resort to trial and error with patients, prescribing several drugs or doses before finding the right one. This is especially true when treating chronic diseases, where drugs often benefit only a minority of patients. To help doctors to optimize their experimental prescriptions, imposing more trial and less error, a company called Opt-e-scrip Inc. (Morristown, NJ, USA) has designed a new form of single-patient clinical trial—a statistically valid test of drug response in one individual. In special situations, an adaptation of Opt-e-scrip's patented trial design can help drug companies to evaluate drugs with fewer patients, less time and lower costs.

### Clinical trial in a box

Opt-e-scrip, according to co-founder Donald P Reitberg, PharmD, is the first company to validate a single-patient clinical trial design. By this he means a mathematical demonstration that the trials discriminate safety and efficacy endpoints in a reproducible way, plus a practical demonstration that they are convenient enough for patients to follow through to the end.

The company, which began operations in the summer of 2000, is preparing a series of clinical trial kits that physicians may prescribe to test US Food and Drug Administration (FDA)-approved drugs in their patients. Opt-e-scrip confines its clinical-trial-in-a-box kits to drugs for diseases that are both chronic and stable, such as attention deficit disorder, hypertension and depression. As designed by Reitberg, a single-patient trial uses a randomized, double-blind, multi-crossover protocol and tests the same symptom-reduction endpoints that the FDA required for drug approval. For him this represents an advance in personalized medicine, more accurate than that which

a doctor can do by trial and error. “You eliminate bias and add true science,” he says, “for the first time offering an evidence-based approach to the problem.”

Opt-e-scrip’s single-patient trial can compare a drug and a placebo, two or three drugs against one another, or different doses of the same medicine. Reitberg and his associates have identified about 20 chronic conditions where doctors routinely prescribe by trial and error. The company’s first kit, scheduled to be on the market in early 2002, compares two drugs for allergic rhinitis. Next will come drug-comparison kits for osteoarthritis and gastroesophageal reflux disease (GERD).

An allergic rhinitis trial begins when a doctor prescribes an Opt-e-scrip self-administered test kit through the company’s mail-order pharmacy. The objective will be to find out which of two FDA-approved drugs best improves the patient’s symptoms. Opt-e-scrip mails the patient a kit containing a month’s supply of the two drugs in blister packages, along with an administration schedule. The patient never knows which drug he is taking; drugs are overencapsulated to look alike, therefore avoiding bias in the results. The patient takes the medications at home and answers a daily questionnaire concerning effectiveness and side effects. (For some kits, a doctor, nurse, parent or teacher may help to determine therapeutic responses.) Opt-e-scrip telephones the patient when needed in order to assure reporting compliance.

The patient takes the drugs in a crossover pattern for 1–6 months, depending on the disease; for allergic rhinitis this is 4 days on one drug, then 4 days on the other. By the end of the trial, the patient experiences four crossover cycles, with the drug order randomized for each cycle.

When the trial ends, Opt-e-scrip breaks the blinding code, analyzes the results and sends its recommendations to the doctor. A Reitberg innovation—and a major reason he received a US patent in June 2001—is

**About 20 chronic conditions have been identified where doctors routinely prescribe by trial and error**

to analyze a patient’s drug-response data in the context of the outcomes of previous patients. His ‘statistical feedback’ technique decreases the variance of statistical estimates. In other words, by weighing the patient’s responses with those of previous trial patients, Reitberg reduces the margin of error in deciding which treatment works best. He says, for example, that feedback might shrink a p value—the probability that a patient’s different responses to drugs are simply due to chance—from 0.05 to 0.01. In this way, “you don’t need as much data to get better estimates.”

### Applications for drug companies

Opt-e-scrip also plans to offer clinical trial services to pharmaceutical companies. Where the usual trial divides patients into drug and placebo control groups, an Opt-e-scrip trial needs only one group, with each patient becoming his own control by taking both agents. The literature describes these as aggregate single-patient clinical trials. Their appeal is that statisticians need far fewer patients to figure out whether a drug works, thus saving time and money. Reitberg particularly likes how aggregate trials benefit participants. “Patients should get the chance to be their own controls,” he declares, “so they will find out if they did better on the drug than placebo.”

But if, as he claims, aggregate single-patient trials offer “better, more rapid estimates of product effectiveness with the fewest number of exposures,” their shortcoming is to offer fewer chances to observe adverse events than trials comparing large populations. This is why the FDA has only rarely favored aggregate single-patient trials: “They usually want to increase exposure to get more safety data.”

But Reitberg points out that there are instances where aggregate single-patient trials make a great deal of sense. First on his list is “where you already have a huge safety database and you’re trying to get a new indication for an old drug.” Since safety was studied when the drug was approved, an aggregate single-patient trial becomes a reasonable way to minimize the cost of testing for a new indication. Drug-superiority studies are another possible application; these projects occur not for regulatory approval, but for marketing purposes, when

## By marketing drugs as single-patient drug trials, companies can help doctors understand when the drugs work best

a company attempts to prove that its drug is more effective than a competitor’s.

Reitberg also recommends the use of aggregate trials when it is advisable to minimize the number of patients exposed, as when testing a drug on children. An orphan drug trial, when there may not be many patients anyway, might be another application. He additionally sees a place for aggregate trials in Phases I and II, where small populations are the norm.

Reitberg hopes that companies will use Opt-e-scrip kits for Phase IV post-market surveillance studies. “The FDA takes a strong position that companies need to go beyond Medwatch and other surveillance methods,” he says. By marketing drugs as single-patient drug trials, companies can help doctors understand when the drugs work best and obtain better post-marketing adverse event data for regulators.

As an achievement in personalized medicine, Reitberg proudly observes that single-patient trials have arrived ahead of prescriptions determined by gene tests. (Opt-e-scrip has filed for international patents covering the use of genomic markers with single-patient trials, however.) With or without genomics, he sees single-patient trials with feedback from aggregate databases as an important new clinical tool. “At the end of the day,” he says, “the whole purpose of this is to be sure that patients get the best outcomes that medicines can provide. Its real beauty is that it maximizes benefit for each individual.” 

Tom Hollon

### Further information

[www.opt-e-scrip.com](http://www.opt-e-scrip.com)

Contact: Donald P Reitberg, PharmD, Vice-Chairman, Co-founder and President of Scientific Affairs, Opt-e-scrip Inc., 25 Lindsley Drive, Suite 203, Morristown, NJ 07960, USA. Tel: +1 973 699 3849, E-mail: donreitberg@opt-e-scrip.com