

# Advances in Single-Patient Trials for Drug Treatment Optimization and Risk Management\*

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Experts in evidence-based medicine consider single-patient trials or “n-of-1” studies to be the highest form of evidence for making individual patient drug treatment decisions. Single-patient trial-based risk management programs for chronic care drugs with recognized safety risks would improve risk/benefit by more reliably identifying individual patients who do not

receive benefit and/or who experience undue short-term adverse events. The widespread use of single-patient trials would also generate a continuously expanding database of prospectively documented effectiveness and safety outcomes that would support population and subgroup risk/benefit assessments, leading to improved prescribing information.

## Key Words

Controlled trials;  
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## INTRODUCTION

Single-patient trials are randomized, usually blinded, multiple-crossover trials in which an individual patient serves as his/her own control to compare two symptomatic treatments for a chronic condition (1). Single-patient trials are appropriate in situations where therapy temporarily relieves manifestations of symptoms, for example, in allergic rhinitis, osteoarthritis, diabetes, gastroesophageal reflux disease (GERD), or major depression. Single-patient trials can be used to compare two different drugs, two different regimens of the same drug, or a drug versus placebo (1).

In the first section, we briefly discuss the history and utility of single-patient trials as a prescribing tool for physicians. We then discuss their potential use within the context of risk management programs for chronic use drugs with known safety risks and provide an example of such a program. Finally, we examine the value of using single-patient trials in the launch of newly approved chronic care drugs as an economical, yet scientifically rigorous, approach to pharmacovigilance that can greatly and rapidly expand the drug knowledge base.

The proposed advancement of single-patient trials involves moving the paradigm from risk management in individuals to risk management in populations. This can now be accomplished due to the development of standardized pharmacy methods for the efficient and reliable as-

sembly of single-patient trials and improvements in information technology that reduce the burden of data collection and analysis.

## SINGLE-PATIENT TRIALS — A BRIEF DESCRIPTION AND HISTORY

Experts in evidence-based medicine consider single-patient trials to be the highest form of evidence for selecting a chronic care treatment for an individual patient (2). Although randomized, controlled clinical trials have long since superseded unsystematic, uncontrolled, clinical observation in evaluating the effectiveness of new therapies in populations, they are rarely used to evaluate individual patients. Most prescribing is still subject to the *post hoc, ergo propter hoc* fallacy; that is, if a patient appears to improve, whatever was given prior to the improvement is assumed to have caused it. In other words, one cannot distinguish between a placebo response, spontaneous change in the patient's condition, or a true response to drug.

In a single-patient trial, the patient usually receives two treatments, one at a time, in random order. To achieve replication, the patient receives each treatment for at least two multiple-day periods. In most single-patient trial designs, consecutive periods are paired, and treatment order is randomized independently for each pair in order to reduce variability due to temporal trends.

Patients ordinarily participate in a single-patient trial as part of their routine medical

care. Since they are not volunteers in an investigational clinical trial, it is desirable to avoid exposing patients to placebo washouts and breakthrough symptoms when comparing two active substances or doses. Instead, a surrogate washout is generally used; that is, effectiveness data captured during the first several days of each treatment period are not included in the analysis. The length of the surrogate washout is determined by the known pharmacokinetic and pharmacodynamic characteristics of the compounds utilized, and prospective statistical evaluation of that washout period during the test validation process.

A commercially available single-patient trial for allergic rhinitis illustrates the design concept (3). As shown in Figure 1, this single-patient trial has four pairs of crossover periods. In each pair, the patient takes Treatments A and B for four consecutive days in random order. Each pair is randomized independently, resulting in 16 possible treatment order sequences. The patient documents effectiveness and adverse events in a daily diary. For the antihistamine products compared in this single-patient trial, only the first day of each treatment period need be considered a surrogate washout period due to short pharmacodynamic effects and biological half-lives.

The initiation and conduct of a standardized, commercial single-patient trial is convenient. The physician simply sends a prescription for the single-patient trial to a suitably equipped and trained pharmacy, specifying a standard test protocol and the two test agents to be used. In most cases, the pharmacist manages patient registration and eligibility screening as part of the fulfillment process. Patient-friendly methods are used for daily data capture, including Web-based data entry screens, an interactive voice recognition system and mark-sense readable paper diaries. Upon completion of the trial, a statistical analysis is rapidly performed and the physician receives both a concise summary and a detailed report of the results. This is then used to guide the patient's ongoing therapy.

Reports of single-patient trials began to routinely appear in the literature during the mid-1980s (4,5,6). Some of the diseases for which single-patient trials have been used to personalize drug therapy are attention deficit/hyperactivity disorder (7,8), hypertension (9,10), chronic pain (11,12), allergic rhinitis (3), and symptoms of GERD (16).

Several approaches to the statistical analysis of data generated by single-patient trials have been reported in the literature. In the early liter-

FIGURE 1

Example of a Study Design: Allergic Rhinitis Single Patient Trial*							
STUDY DAY							
1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32
Crossover Pair 1		Crossover Pair 2		Crossover Pair 3		Crossover Pair 4	
-Days 1 to 4				Patient takes Treatment A			
-Days 5 to 8				Patient takes Treatment B			
-Days 9 to 12				Patient takes Treatment B			
-Days 13 to 16				Patient takes Treatment A			
-Days 17 to 20				Patient takes Treatment B			
-Days 21 to 24				Patient takes Treatment A			
-Days 25 to 28				Patient takes Treatment A			
-Days 29 to 32				Patient takes Treatment B			

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ature, subjective interpretation based on descriptive statistics and graphs were the norm (20). A more rigorous approach involves reducing repeated observations within a period to a single value in order to eliminate the potential issue of autocorrelation, then performing a randomized block analysis in which each randomized pair is considered to be a block (21). An analysis using individual observations based on an autoregressive process of order 1 has also been proposed (22); however, the test is based on large sample theory which may not be appropriate for most single-patient trials. A hierarchical Bayesian approach has also been described, combining individual and population estimates to improve predictive value (15). We have recently applied a frequentist hierarchical model to the analysis of single-patient trials for gastroesophageal reflux disease and allergic rhinitis (3,16).

Although it has long been known that the effectiveness and tolerability of a given drug can vary considerably among patients, only in recent years has the expectation of routine, evidence-based, personalized pharmacotherapy received much attention, mainly due to the potential role of genomics and proteomics in drug discovery and development, and the correlation of these markers to benefit and risk. Single-patient trials have not received the publicity garnered by genetic-based methods, perhaps because few clinicians have had access to the expertise and resources needed to design, conduct, and analyze a single-patient trial. However, the development and validation of standardized single-patient trials for appropriate disease categories, along with advances in modern pharmacy packaging and clinical data capture technologies, now make single-patient drug trials a convenient and cost-effective option in routine medical practice.

It should also be noted that, since genetics alone do not fully explain intraindividual variability (13), single-patient trials can continue to be of value for therapeutic personalization once genetic-based prognostic testing becomes a reality.

## SINGLE-PATIENT TRIALS IN RISK MANAGEMENT

Current risk management programs seek to influence physician and patient behavior towards stricter adherence to drug labeling provisions and heightened vigilance for the manifestation of serious adverse events. The inclusion of “black-box” warnings in the drug’s label is the simplest approach. A more stringent mechanism is a registration procedure for healthcare providers, along with hard-to-ignore educational materials and warnings for both the physician and patient. While such programs undoubtedly reduce the size of the population at exposure to risk by discouraging inappropriate prescribing, they may also be blunt instruments, discouraging physicians from prescribing the drug for patients in whom the potential benefit may actually outweigh the risk.

A risk management program that requires or encourages a single-patient trial as the patient’s first prescription for the drug would provide a the physician with an objective patient monitoring tool, allowing medication to be discontinued if the drug proves therapeutically unnecessary or causes undue adverse events. The advantages of a risk management program based on single-patient trials are readily apparent:

1. Physicians can receive structured feedback on the patient’s response to therapy and adverse events, recorded on a daily basis,
2. Since placebo or another active drug is used as a comparator, single-patient trials provide a scientifically reliable means of discerning between the effects of the drug and either placebo response or normal temporal variability, and
3. Customer support activities associated with the conduct of a single-patient trials program can improve communication with patients, for example, offering access via a toll-free number to a healthcare professional who can answer questions and/or alert the prescribing physician to any issues that may need attention.

With current risk management programs based on simple observation, only unequivocal nonresponders can be identified. By comparing a given drug against an appropriate control in a

single-patient trial, many placebo-responders can also be identified and discontinued, further reducing the population-level risk. Since placebo response rates on the order of 20% to 40% are common for many chronic care drugs, single-patient trials can have a substantial impact in reducing unnecessary exposure to risk. In cases where the physician is reluctant to place the patient at risk of disease exacerbation by using a placebo, a low-toxicity alternative treatment or a lower dose of the drug could be used as the comparator.

Risk management programs based on single-patient trials technology provide a rational basis for restricting access to drugs of concern; that is, the overall risk/benefit ratio can be significantly improved simply by eliminating those patients who demonstrate no benefit. Although no test method can distinguish drug responders from nonresponders with 100% accuracy, single-patient trials can provide good specificity and sensitivity in this regard, particularly when historical data from similarly designed single-patient trials are used to enhance the power of individual single-patient trials analyses (3,15,16). Prior experience with single-patient trials for the treatment of GERD and allergic rhinitis indicate that it is often possible to achieve approximately 80% to 90% power to detect a clinically significant difference from placebo while assuming a 5% risk of obtaining a false-positive result (3,16).

Single-patient trials can also serve to make a drug more widely available to appropriate patients without incurring undue public health consequences. Single-patient trial patients are registered and screened for eligibility, then monitored for symptoms and adverse events on a daily basis. With these mechanisms in place to document appropriate prescribing and heightened vigilance for effectiveness and adverse events, physicians may be less reluctant to prescribe drugs with known risks.

### A THEORETICAL RISK MANAGEMENT EXAMPLE

Alosetron hydrochloride is indicated for the symptomatic treatment of diarrhea-predomi-

nant irritable bowel syndrome (IBS) in women. This drug was temporarily removed from the market in 2000 due to spontaneous reports of ischemic colitis and complications of constipation, and returned to the market in 2002 with revised labeling and a risk management program. The revised labeling redefines the target population as females with severe IBS who do not have a history of constipation or other lower gastrointestinal symptoms. As discussed in the Food and Drug Administration's press release of June 7, 2002, the risk management program is intended to ensure that only patients in this restricted target population receive alosetron (17). It also seeks to raise the level of vigilance by healthcare providers and patients with respect to the emergence of the abovementioned serious adverse events.

Single-patient trials can potentially offer an improved, evidence-based means of reducing unnecessary population exposure to alosetron by allowing physicians to identify patients who are nonresponders and placebo responders and thereby discontinue their therapy. Single-patient trials can also facilitate needed and appropriate drug exposure by identifying responders. The Food and Drug Administration's retrospective analysis of the pivotal trials for this drug indicate that, by one primary measure, 50% of patients in the restricted target population obtain meaningful symptomatic relief on alosetron, as compared to about 30% of placebo patients (18). Therefore, it appears likely that the majority of patients receiving alosetron long-term under the current risk management program may, in fact, be nonresponders or placebo responders, neither of which receives benefit to offset the risk of their exposure to alosetron. By the same token, this population-based approach to risk management may have had the effect of making alosetron unavailable to patients in whom it would prove to be both effective and well tolerated.

The clinical trials conducted for the regulatory approval of alosetron (19) suggest that it may be feasible to design a single-patient trial for this purpose since efficacy is measured using

patient self-reported endpoints over a reasonable timeframe.

With single-patient trials as a monitoring tool, physicians could, in theory, more confidently introduce a greater number of suitable patients to “black box” drugs such as alosetron hydrochloride because single-patient trials can serve to reduce unnecessary risk to individuals. Only effectiveness-documented, appropriate patients will continue therapy. It is of interest to note that estimates of effectiveness rates for alosetron and placebo in the original clinical trial population are not materially different than those for the restricted population. Therefore, a more effective public health strategy may be to allow a somewhat broader population to receive a first prescription for alosetron in the form of a single-patient trial, but to limit refill prescriptions to those patients in whom alosetron proves superior to placebo, or to a lower-risk active comparator. Overall usage may actually be increased, rather than reduced, by the availability of single-patient trials, but only evidence-appropriate, risk-managed patients would receive continuing treatment. Therefore, increased usage will not result in undue population exposure.

### SINGLE-PATIENT TRIALS FOR POSTMARKETING SURVEILLANCE AND PHARMACOEPIDEMIOLOGY

Single-patient trials also offer a significant opportunity to rapidly expand the limited knowledge base for newly approved chronic care drugs. A new product market introduction that incorporates the widespread prescribing of single-patient trials would effectively create an ongoing, controlled, large-scale clinical trial under real-world conditions. This would, in theory, be of great value since the clinical trials conducted under an Investigational New Drug for marketing approval typically exclude a significant segment of the target population on the basis of age, concurrent illnesses or concomitant medication use, and are rarely large enough to reliably identify population subsets in whom the drug tends to be ineffective and/or poorly tolerated. A database of single-patient trial re-

sults would also offer an enhanced opportunity to detect rare but important adverse events and drug interactions under controlled conditions.

As discussed earlier, the most appropriate analysis of an individual single-patient trial follows that of a randomized block design, with the treatment pairs as blocks and the periods as plots. However, it is readily apparent that a series of single-patient trials, when randomized using an appropriate common mechanism, jointly constitute a multiple crossover design; that is, a crossover design in which each patient receives each treatment more than once. Unlike the more common two-period design, a multiple crossover design can provide efficient estimates in circumstances where carry-over effects are found.

Single-patient trials can often be performed at a reasonable price; that is, they are often no more expensive than the cost of a newly introduced drug for the duration of the test. Moreover, since no investigational drugs are being used, it should be possible to obtain reimbursement for insured patients. In other words, the operational costs associated with a large postapproval program of single-patient trials will be quite reasonable in most cases.

### CONCLUSIONS

For chronic use drugs, single-patient trials can serve as the basis for an effective risk management program. Such a program would retain key components found in conventional risk management programs, including measures to ensure proper prescribing and heightened vigilance for emerging adverse events. By restricting drug exposure to only those patients who actually demonstrate benefit, a single-patient trial-based risk management program can be expected to produce a better risk/benefit profile than conventional programs.

A single-patient trial-based risk management program is also, in effect, a large, postapproval surveillance trial. The efficacy and safety data can serve to enhance the knowledge base concerning a newly approved drug at a much lower cost and with far higher quality than conventional postmarketing surveillance trials, and can

help practitioners gain controlled experience with the drug. Therefore, it may be advantageous to conduct a single-patient trial program even when there are modest safety concerns regarding a new drug.

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