

## THE ACTUAL USE TRIAL: A DESCRIPTION OF DESIGN PRINCIPLES AND METHODS

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### ABSTRACT

The actual use trial is a method for assessing safety of a prescription drug under conditions resembling non-prescription use. Thus, it is generally a key study in an application for the over-the-counter (OTC) switch of a drug in the U.S. Research models commonly used in pharmaceutical development or oversight (efficacy trials, phase 4 studies, and passive surveillance systems) are designed to answer other questions and offer only limited data about the suitability of a switch. We discuss study design elements that contribute to an understanding of the consequences of allowing consumers to carry out the functions normally performed by a physician (diagnosing, prescribing, and monitoring).

**Key words:** Actual use, OTC switch, observational studies

### INTRODUCTION

The pharmaceutical research literature does not contain a well articulated, widely accepted model for conducting research on safety in actual use. The purpose of this paper is to describe the design elements that must be part of a true actual use safety trial and consider certain scientific issues associated with an observational study. Although the principles we will discuss can be applied to safety assessment in any setting, we will focus on the application that is arguably the most complex and difficult: actual use safety trials to support an OTC switch.

The actual use trial (AUT) is a specialized safety and use trial. It may be thought of as an anticipatory observational trial, one in which carefully designed operations are implemented to create a setting for use that does not currently exist (such as over-the-counter sale of a drug presently available only by prescription). Subjects are observed in that setting to provide a forecast of the behavior, and consequences of that behavior, of consumers under OTC conditions.

When a drug is licensed for non-prescription sale, the consumer performs the functions that were formerly managed by a physician. Under these new circumstances, the consumer must make a self-diagnosis of the condition the drug is intended to treat, evaluate any contraindicating conditions, decide how to use the drug, monitor the therapeutic and adverse consequences of

use, and modify or discontinue use (or seek medical consultation) when recommended. One of the key regulatory questions in an over-the-counter (OTC) switch is whether subjects can correctly perform those functions in a way that does not create an unacceptable public health risk (an incremental risk that outweighs any incremental benefit arising from broader, easier access). A properly designed and conducted AUT can help answer that crucial question.

An AUT comes after any necessary preliminary studies have been performed. The most important of these are efficacy trials at the dose planned for the OTC version of the drug, label comprehension studies to ensure that the label is understood by the general public, and self-selection trials which demonstrate that people who have the condition in question and intend to treat it themselves can make a proper selection of the drug.

## **BACKGROUND**

Why is the AUT needed? None of the other methods in general use for the assessment of pharmaceutical products provide data to answer the question, "What are the public health implications of removing the healthcare professional from the process of diagnosing the problem, prescribing the drug, and monitoring its use?" We will briefly examine the alternatives.

### **Efficacy trials.**

Experimental trials undertaken to demonstrate a drug's efficacy always include a safety assessment. However, there are several reasons why that assessment is not adequate for estimating the safety of the drug under OTC conditions. First, subjects in efficacy trials do not make a decision to self-treat the condition for which they take the drug, so they represent a different population from self-treaters. Secondly, experimental subjects are highly selected to produce a homogeneous sample and thereby increase experimental power. However, the diversity of medical history, concomitant health conditions, and concurrent use of other drugs that are disadvantages in an experiment are crucial in an AUT where an important purpose is to permit generalization of findings to the entire potential OTC user population. Thirdly, experimental subject use of the drug is carefully controlled by protocol, with limited opportunity for subjects to adapt their use or make errors in dosing. Thus, they are not exposed to the same potential risk conditions that an OTC drug user faces; something an AUT permits. Fourthly, efficacy researchers have considerable freedom in gathering data about outcomes of treatment, as there is no need to simulate natural use patterns and therefore no threat of reactivity in measurement (that is, measurement of use affecting subsequent use). Finally, a number of other steps are taken in an efficacy trial that are irrelevant to an observational study but may interfere with natural use of a drug, such as random assignment of subjects to study conditions and blinding of subjects to the condition they are in.

### **Registries and epidemiologic studies.**

Other methods for evaluating safety in actual use include passive surveillance systems (such as the Food and Drug Administration's MedWatch system) and epidemiologic studies. While

these systems and studies perform a useful signal detection function, they are inadequate to estimate rates of noncompliant product use, they typically have too little data in the system to answer anything other than the broadest questions, and they are slow - it takes a long time to accumulate enough data to generate useful findings.

#### **Phase 4 trials.**

Post-marketing studies come the closest to providing data relevant to an OTC switch. Because they monitor actual drug use, they may provide useful comparative data. However, the focus of these studies is on real prescription use of the drug and they are therefore of limited value in forecasting the nature and consequences of non-prescription use.

The AUT is designed specifically to evaluate the public health implications of an OTC switch. It is not experimental, and therefore can avoid the limitations on generalizability associated with efficacy trials. It is observational, but relies on a set of operations to structure the conditions under which the observations are made. The scientific challenge of an AUT is to conceive of and implement those conditions so that the findings of the study can forecast actual anticipated OTC use. In essence, the fundamental task is to sample from a population that does not yet exist, but which can be defined according to a set of operations.

### **DESIGN PRINCIPLES**

Every OTC switch project has its own challenges and complexities, and the design of an AUT needs to take them into account. Therefore, the specifics of design will vary from project to project. However, there are some general principles that should guide the design. The several design elements described below are based on the general principle that the process of recruiting and enrolling subjects, as well as conditions of use and follow-up, should be as naturalistic as possible. However, even properly designed use trials fall short of completely naturalistic observation because of the necessary imposition of procedures required to conduct science and protect subjects' rights. For example, enrollment, informed consent, and data collection procedures inevitably reduce the naturalistic character of the subject's experience. The degree to which these elements must be compromised depends on the purposes of the trial, but the more closely the design hews to these design features, the more representative of actual anticipated use it will be.

#### **Self-selection into the trial.**

Subjects in a true actual use trial should be allowed to make the choice about participating in the trial in much the same way as they would make the decision about using the product in a non-research setting. That is to say, they should be allowed to decide about whether to use the drug in as normal a way as possible.

If a comparison condition is used in the trial, subjects should be allowed to choose which of the conditions to enter based on a procedure that is as similar to the normal process

of drug selection as possible. Randomization of subjects to conditions is inconsistent with the observational nature of an actual use trial. Furthermore, subjects cannot be blinded to treatment conditions, because subject choice (first, about whether to self-treat and secondly, which treatment to select) is a crucial component of actual use.

**Enrollment sites.**

Subjects should be enrolled where they normally get their drugs. For OTC switch studies, the logical place for enrollment is the pharmacy. It is true that in the U.S., OTC drugs can be purchased in other places as well, but the pharmacy represents the best compromise between the need to mimic the OTC setting and the requirements of data collection, drug monitoring, and obtaining subject consent.

The main alternative to pharmacies is a temporary 'storefront', often located in a shopping mall. Although the storefront lacks the naturalism of the pharmacy, it may provide somewhat greater control over the enrollment process. Studies using storefronts generally have relatively few sites staffed by researchers whose only function is carrying out the procedures dictated by the protocol, unlike the pharmacy staff who also carry on their normal retail functions.

**Enrollment strategy.**

The enrollment sequence should be designed to interfere as little as possible with the attempt to evaluate the normal process of drug selection. For an OTC switch safety trial, it is crucial that subjects be allowed to decide about whether the drug is appropriate for them based on the information they would normally obtain from the package or spontaneously seek out from the pharmacist or others. If the consent process comes too early in the enrollment process - before that decision has been made - more information is made available to the subject than is the case for a real OTC selection. One goal of enrollment is to determine whether subjects can make proper selection and purchase decisions based on the label.

In addition to proper sequencing of the data collection and consent procedures needed during enrollment, the entire enrollment process should be kept as short and simple as possible, to reduce dropout bias arising from the research procedure itself. AUT designers should seek to gather only critical information at enrollment (including data that would permit a comparison of enrollers and non-enrollers), and defer as much information as possible to later stages of data collection.

**Drug packaging.**

The drug should be made available to prospective subjects in a package that is as similar to the final marketed package as possible. For drugs intended to be switched, the proposed (and tested) OTC label should be used for the trial. This stage of research may be viewed as the final behavioral validation of the cognitive comprehension studies that were performed before the study. If a version of the final packaging cannot be produced, the study package should at least look like a real marketed drug to make the product credible.

**Subject recruitment.**

The more closely subject recruitment procedures reflect the strategies that will be used in future OTC customer recruitment, the more likely it is that the final sample will resemble the ultimate user population. In practice, the most efficient advertising is in media that serve the area around the participating pharmacies.

Experimental studies typically use active methods for recruiting subjects, often from patient records or other registries. In contrast, recruitment for an AUT should use passive measures, where entry into the trial is based on individuals' initiative in inquiring about the study from the advertising they encounter. That approach increases the likelihood that study subjects will resemble the ultimate OTC consumer. One consequence of this strategy is that the researcher has less control over the rate of enrollment and fewer tools for increasing the rate.

**Appropriate follow-up data collection.**

Collecting information about the subject's use of the drug, and the outcomes of that use, is complicated by the need to gather data in ways that are least likely to affect subsequent use of the drug, so that the collection of data does not change the behavior that is being evaluated. The least reactive and obtrusive data collection method is generally the post-use interview. The interview should be initiated as soon after the use of the drug as possible, and should be designed to obtain the degree of detail that is appropriate, given the length of time between use and interview.

The design and timing of the interview are relatively straightforward for drugs used to treat acute conditions. For drugs that are used to treat chronic or intermittently recurring conditions, it is important to structure the questions to be as neutral as possible, to reduce the social desirability component of subjects' responses. It is also good practice to time interviews so that they do not prompt subjects to take an action that they might otherwise neglect, such as obtaining a new supply of medication.

Diary cards have a long history in randomized trials, but pose a problem for an observational study. Any study requirement that reminds subjects of the fact that they are in a trial runs the risk of affecting later use. Of course, interviews remind subjects that they are, in fact, subjects, but the fact that they occur infrequently and are initiated by the researcher produces less reactivity than having to remember to make entries either daily or for each instance of use. Data completeness and quality are also a problem for both experimental and observational studies, but the methods that can be used to remind subjects about their diary duties in an efficacy trial only serve to increase the threat of reactivity in an AUT.

**All-comers trials.**

Because the intent of these trials is to assess safety of the drug when it is used by those who believe the drug is right for them, it is important to limit the exclusion criteria for participation to the minimum required to ethically conduct the study. This stands in contrast to experimental

trials, where rigorous inclusion and exclusion criteria are imposed to reduce between subject variability and increase experimental power.

### **Large samples.**

Because AUT samples tend to be much more diverse than efficacy trial samples (in medical history, concomitant medications, and other circumstances relevant to the use of the drug), it seems prudent to gather data from a larger group of subjects. Larger sample sizes permit reasonably powerful comparison among subgroups in the sample (for example, adolescents v. the rest of the group, or males v. females).

### **TYPICAL METHODS FOR AN AUT**

This brief overview of AUT methods is based on a pharmacy-enrollment model. It is the one we are most familiar with and is the most naturalistic. A typical study comprises two phases, enrollment and follow-up. The enrollment phase begins with recruitment efforts in the communities where trained enrollment sites are located. Advertising for the study can range from in-store signs to metropolitan television, radio, and newspaper advertisements. It is most cost-effective when it is concentrated in the areas adjacent to the enrollment site and relies on local newspaper advertising and mailings directly to households in the zip codes surrounding the pharmacy. The content of the advertisement is controlled in large measure by regulation, but generally contains a reference to the condition the drug treats and an invitation to telephone a toll-free number for more information.

Those who respond to the advertisement are directed to the nearest enrollment pharmacy. Little or no screening is done during that first contact so as to refrain from interfering with the subject's selection decision. Respondents are scheduled for a pharmacy visit, where they begin the actual enrollment process.

Prospective subjects who enter the pharmacy are shown a package similar to the anticipated OTC box, with the Drug Facts label, and asked whether it is right for them. They are then asked some questions about their medical history relevant to the drug (to assess the accuracy of their selection decision) and a few key demographic questions. Only then do those who indicated that the drug was right for them read the informed consent document. Those who consent are then given or sold the study drug.

The follow-up phase of the study begins when the subject leaves the pharmacy with the study drug. The length of the follow-up phase is determined by the elements of the label that need testing, such as a period of recommended use, a dose adjustment, or a requirement to consult a health care professional. Subjects are free to use the drug during this phase however they choose. Subject use patterns are never driven by the protocol. They are also free to return to the pharmacy at any time for additional drug, but are not required to do so. They are also at liberty to decide not to use the drug at all or to discontinue and resume taking the drug at any time.

Follow-up interviews are conducted rarely but periodically over the use period. They should be

scheduled to avoid times when the subject is directed by the label toward some action (such as talking with their doctor), to reduce the likelihood that the interview will remind them of something they would not have remembered otherwise. The interviews are generally short and use non-directive questions to determine whether an adverse event might have occurred. Adverse events are evaluated and followed according to regulatory guidelines.

At the conclusion of the use period, a final interview is conducted. This interview may contain questions about why they used the drug incorrectly during the study, as there is no subsequent use of the drug which those direct questions might affect. No further drug purchases are permitted. After all subjects have completed the trial, subjects are compensated for their drug purchases during the trial, something they were not informed of earlier.

### **SUMMARY**

It is never possible to create a truly natural setting for an AUT. The requirement to gather data while protecting subject rights creates profound artificiality in the drug transaction. Nevertheless, it is important to design these trials in a way that preserves the real-life flavor of key elements of the process, such as subjects' selection and use decisions. The more the research can stay out of the way of subject behavior, the more likely it is that the findings will reflect the way consumers will behave once the drug is made available for non-prescription use.

It should be clear from this description that the AUT is fundamentally different from an efficacy trial. Neither research model is any more or less scientific than the other - they are simply different models designed to answer different questions. Therefore, any attempt to create a hybrid (such as a so-called actual use efficacy trial) is doomed, as the design features of the two studies are irrevocably at odds. The chimera that results from such an attempt will correctly be seen either as a flawed experimental trial (lacking the usual measures to enhance power) or a deficient observational study. However, taken on its own terms, the actual use trial is a useful tool for the pharmaceutical researcher.

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