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Review Article

A Comprehensive Review Clinical Trials: Phase IV

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ABSTRACT

A phase IV clinical study is an important step in the monitoring of a new medicine after it has been approved for commercial distribution. It is a key component of post-marketing research that focuses on real-world efficacy and pharmacovigilance, not only continuing but also supplementing prior studies. Phase IV clinical trials change greatly from earlier research phases in terms of study design, criteria, and scientific demand. Phases I through III primarily test the drug's safety profile on a smaller scale, as well as its efficacy in a controlled setting of an RCT. Phase IV investigations, on the other hand, promise to identify even rarer ADRs that may have gone undetected in prior trials, as well as to assess whether the new medicine establishes its benefit on the open market, in interactions with other pharmaceuticals, and in demographic groups who were not previously accepted to the research. The goal of this article is to build up phase IV clinical studies in combination with preceding preclinical experiments to gain a better sense of the lengthy road a medicine takes—not only until it hits the market, but also afterward. Other objectives include demonstrating the relationship with various aspects of post-marketing research, investigating the present function of phase IV studies, and researching the extent to which the current situation of phase IV clinical trials satisfies needs.

INTRODUCTION

A clinical trial is a systematic process that is intended to find out the safety and efficacy of a drug/device in treating/preventing/diagnosing a disease or a medical condition (1,2). Clinical trial includes various phases that include phase 0 (micro-dosing studies), phase I, phase II, phase III, and phase IV (3). Phase 0 and phase 2 are called exploratory trial phases, phase 1 is termed the non-therapeutic phase, phase 3 is known as the therapeutic confirmatory phase, and phase IV is called the post-approval or the post-marketing

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surveillance phase. Phase 0, also called the micro-dosing phase, was previously done in animals but now it is carried out in human volunteers to understand the dose tolerability (pharmacokinetics) before being administered as a part of the phase I trial among healthy individuals. Approximately 20% of drugs acquired new black box warnings post marketing, and IV% of the drugs were ultimately withdrawn for safety reasons. (6) In 2007, the Food and Drug Administration was authorised by the Food and Drug Administration Amendment Act (FDAAA) (7) to require post marketing clinical trials to address safety concerns regarding a given drug. Compared to premarketing phase I–III trials, phase IV studies evaluate drug safety in a real-world setting, which may provide evidence to ensure or further refine the safety of approved drugs. (5.8,9) However, little is known about the characteristics of contemporary phase IV clinical trials and whether these studies are of sufficient quality to advance medical knowledge in pharmacovigilance.

OBJECTIVE

Phase IV clinical trials are conducted after a drug or medical device has been approved by the FDA and is available on the market. These trials are also known as post-marketing surveillance studies, and they are designed to monitor the safety and efficacy of the drug or device in a larger population and over a longer period of time than was possible in the pre-marketing clinical trials.

METHODS

A data set of 19 359 phase IV clinical studies registered in ClinicalTrials.gov was downloaded. The characteristics of the phase IV trials focusing on safety only were compared with those evaluating both safety and efficacy. We also compared the characteristics of the phase IV trials in three major therapeutic areas (cardiovascular diseases, mental health and oncology). Multivariable logistic regression was used to evaluate factors associated with the use of blinding and randomisation.

PHASE IV TRIALS

Once a drug is approved, the FDA may require that a sponsor conduct a phase IV trial as a stipulation for drug approval, although the literature suggests that less than half of such studies are actually completed or even initiated by sponsors. (10) Phase IV trials, also referred to as “therapeutic use” or “post-marketing” studies, are observational studies performed on FDA-approved drugs to:

1) Identify less common adverse reactions,
2) Evaluate cost and/or drug effectiveness in diseases, populations, or doses similar to or markedly different from the original study population.

Limitations of pre-marketing (eg, phase III) studies become apparent with the statistic that roughly 20% of drugs acquire new black box warnings post-marketing, and approximately IV% of drugs are ultimately withdrawn for safety reasons. (11,12) As described by one pharmacoepidemiologist, “this reflects a deliberate societal decision to balance delays in access to new drugs with delays in information about rare adverse reactions.” (13) Over the past decade, there has been a steady rise in voluntarily and spontaneously reported serious adverse drug reactions submitted to the FDA’s MedWatch program, from 150 000 in 2000 to 370 000 in 2009.(14) Reports are submitted directly by physicians and consumers, or indirectly via drug manufacturers (the most common route). Weaknesses of this post-marketing surveillance are illustrated by recent failures to quickly detect serious cardiovascular events resulting from the use of the anti-inflammatory medication Vioxx® and prescription diet drug Meridia®. It was only after the European SCOUT (Sibutramine Cardiovascular OUTcome Trial) study, driven by anecdotal case reports concerning cardiovascular

safety, that the FDA withdrew Meridia® from the market in late 2010.(15)

The most common criticisms of the FDA's post-marketing surveillance are:

1. The reliance on voluntary reporting of adverse events, resulting in difficulty calculating adverse event rates because of incomplete data on total events and unreliable information on the true extent of exposures;
2. The trust in drug manufacturers to collect, evaluate, and report drug safety data that may risk their financial interests;
3. The dependence on one government body to approve a drug and then actively seek evidence that might lead to its withdrawal. (10,13)

Proposed solutions include the establishment of a national health data network to oversee post-marketing surveillance independent of the FDA-approval process, (14) preplanneds meta-analyses of a series of related trials to assess less-common adverse events, (15) and large-scale simple RCTs with few eligibility and treatment criteria (ie, Peto studies). (16)

Phase IV clinical trials can be used to:

- Identify rare or long-term side effects
- Evaluate the drug or device in new patient populations or for new uses
- Compare the drug or device to other available treatments
- Gather more information about the cost-effectiveness of the drug or device

Phase IV clinical trials can be observational or interventional. Observational studies simply observe participants and collect data on their health outcomes. Interventional studies involve assigning participants to different treatment groups, such as receiving the drug or device being studied or a placebo. (17,19)

Importance of phase IV clinical trials

Phase IV clinical trials are an important part of the drug development process. They help to ensure that drugs and medical devices are safe and effective for the general population.

For example, a phase IV clinical trial of a new cancer drug might be conducted to monitor the long-term safety of the drug and to identify any rare side effects that were not detected in the pre-marketing trials. A phase IV clinical trial of a new type of insulin might be conducted to compare it to other available insulin products in people with diabetes.

Benefits and risks of participating in phase IV clinical trials

The benefits of participating in a phase IV clinical trial include:

- Access to the latest medical treatments
- The opportunity to help others by providing important information about the safety and efficacy of new drugs and medical devices
- Regular medical care and monitoring from experienced healthcare professionals

The risks of participating in a phase IV clinical trial include:

- The possibility of experiencing side effects from the drug or device being studied
- The possibility of not receiving the most effective treatment available
- The time and commitment required to participate in the trial

If you are considering participating in a phase IV clinical trial, be sure to talk to your doctor about the benefits and risks involved. (18)

Examples of phase IV clinical trials

Here are some examples of phase IV clinical trials:
A trial to study the long-term safety of a new cancer drug

- A trial to compare a new type of insulin to other available insulin products in people with diabetes
- A trial to evaluate the effectiveness of a new surgical device in people with heart disease

- A trial to study the cost-effectiveness of a new drug for treating migraines

DESIGN OF PHASE IV CLINICAL TRIALS (19,20)

The design of a phase IV clinical trial will depend on the specific goals of the trial. However, there are some general principles that apply to all phase IV trials. Phase IV trials are typically larger and longer in duration than pre-marketing clinical trials. This is because they are designed to monitor the safety and efficacy of the drug or device in a larger population and over a longer period of time. Phase IV trials can be conducted in a variety of settings, including hospitals, clinics, and private practices. The specific setting will depend on the goals of the trial and the type of drug or device being studied. Phase IV trials can be open-label or blinded. In an open-label trial, participants know whether they are receiving the drug or device being studied or a placebo. In a blinded trial, participants do not know which treatment they are receiving. The most common type of phase IV trial is a registry trial. Registry trials are observational studies that collect data on participants from routine clinical practice. Registry trials are often used to monitor the long-term safety of drugs and devices, as well as to compare different treatments. Another common type of phase IV trial is a comparative trial. Comparative trials compare the drug or device being studied to another available treatment. Comparative trials can be observational or interventional.

Analysis of phase IV clinical trials

The data from phase IV clinical trials is analyzed and reported in a similar way to the data from pre-marketing clinical trials. However, there are some additional considerations for phase IV trials.

For example, phase IV trials often use observational data. This can be challenging to analyze because the data may not be as well-controlled as the data from interventional trials. In addition, phase IV trials often involve large numbers of participants and long follow-up periods. This can make it difficult to identify and report on all of the relevant safety and efficacy data.

Challenges of conducting phase IV clinical trials

There are a number of challenges associated with conducting phase IV clinical trials. These challenges include:

- The high cost of conducting large-scale clinical trials
- The difficulty of recruiting and retaining participants in long-term trials
- The challenge of analyzing and reporting observational data
- The need to balance the need for safety monitoring with the need to minimize the burden on participants

Additional considerations for phase IV clinical trials (19)

In addition to the challenges listed above, there are a number of other considerations that should be taken into account when designing and conducting phase IV clinical trials. These include:

- The ethical implications of conducting trials with patients who are already receiving treatment
- The need to protect the privacy of participants
- The need to communicate the results of trials to participants and healthcare providers

Despite the challenges, phase IV clinical trials are an essential part of ensuring the safety and efficacy of drugs and medical devices for the general population.

Strengths and limitations of this study

- We provided a comprehensive descriptive assessment of the current portfolio of phase IV clinical trials evaluating drug safety in the ClinicalTrials.gov registry.

- We employed logistic regression models to determine the factors associated with the use of blinding and randomisation in phase IV clinical trials which evaluated drug safety.
- We followed a strict analysis process that was widely used in analysing the data from ClinicalTrials.gov to arrive at convincing results.
- Some clinical trials were not registered in ClinicalTrials.gov.
- There were some unavoidable missing data for certain data fields which might introduce some bias into the results.(20)

CONCLUSION

Phase IV clinical trials are an important part of the drug development process. They help to ensure that drugs and medical devices are safe and effective for the general population. By monitoring the safety and efficacy of drugs and devices over a long period of time, researchers can identify any rare or long-term side effects, as well as how the drug or device performs in different patient populations and for different uses..

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