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Role of Post-Marketing Surveillance in Drug Safety

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ABSTRACT
Creating resilience and safety for patients during and after clinical trials is a key task in the development of a new drug. However, clinical trials provide important information on the efficacy and safety of drugs. But it is probably not enough to have extensive evidence about the safety of the drug at the time of authorization because previous clinical trials have not been able to guarantee that the drug will not have harmful side effects when it comes to the market. The main purpose of the practice, post-marketing research to confirm the negative and positive effects of drugs that were previously unknown. Post-sales surveillance helps monitor drug safety after passing clinical trials and when drugs arrive on the market. The review includes information on clinical trial categories as well as various approaches to determine the likelihood of adverse drug testing (ADR) and drug safety monitoring.
Keywords: *Post-marketing surveillance (Phase IV), Drugsafety, Adverse drug reaction, Clinical study*

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INTRODUCTION

Post-marketing surveillance or commonly referred to as Phase IV clinical trials where product safety is monitored when a drug molecule arrives on the market, after successful completion of clinical trials [1]. Clinical trials are investigative research that explores new treatments or new approaches associated with existing treatments to determine their effect. The primary goal of clinical trials is to detect new ADRs or mutations related to the re-emergence of ADRs that are always related to certain existing drugs [2]. The results of Phase IV studies can be extended to Phase II and III studies to increase the index and its conversion to dosages. It systematically investigates anthropoid subjects to evaluate the safety and efficacy of any new drug. The clinical trial process begins with the submission of an application for a new investigative drug (IND) by a drug developer to the Food Drug Administration (FDA), after the completion of a pre-clinical trial. If the FDA approves the IND application, then the drug developer may initiate clinical trials of the safety and efficacy of the drug [3]. The ultimate goal of drug development is therefore to prepare new, harmless and effective molecules to cure human disease [4].

Phases of clinical examination

The approval of the Food Drug Administration is very important in the marketing of the re-branded drug on the market. In order to use the drug for commercial purposes, it requires three effective FDA-approved clinical trials [3].

Phase 0 clinical trial

Phase 0 trials are also known as low-dose human studies. A few (10-15) volunteers were enrolled in the study. Phase 0 studies do not provide data, safety and efficacy of the drug as the dose is too low to cause any treatment effect. The low dose helps researchers select the best drug volunteer in a clinical trial by providing early human pharmacokinetic (PK) and bioavailability data. The trial period for phase 0 can be up to one week. These studies help to complete the treatment of patients before they reach class I. [5,6] The first phase study determines the probability of the production of drug cells or a biological product controlled by the drug testing and research center (CDER [7].

Phase I clinical trials (Safety screening):

The new drug was introduced for the first time in human phase I clinical trials. The primary goal of phase I clinical trials is to evaluate drug protection and to calculate the appropriate dose to continue the study [8]. The Phase I clinical trial collects dosage or treatment information after taking the dose and evaluates side

effects or treatment-related problems. If harmful complications are detected in the first phase of clinical trials, the FDA may refer to conducting clinical trials that prevent drug research from progressing to phase II testing [3]. Phase I clinical trials are conducted to determine the best dose of a new drug with very few side effects, The goal is to determine safety and dosage form. This study usually involves a small number of volunteers (usually 10-100). It usually involves volume variation, also known as volume increase studies. The main objective of this study was to evaluate the protection (Pharmacovigilance), tolerance, pharmacokinetics and pharmacodynamics of the drug. The duration of the first phase of clinical trials reaches a few months. During the phase, I research researchers often evaluate young drug users in healthy volunteers and monitor the side effects of the drug. But because of the limited number of volunteers in the study, the unusual side effect may not be eliminated in the study [9].

Phase II clinical trial (Fulfillment of efficacy):

A phase II trial, also known as a clinical trial trial. This study is usually larger than the I phase of the study and was performed on a small number of volunteers with a disease of interest [9]. Phase II studies were conducted to monitor and evaluate the initial activity of the anti-infective compound. Any data are collected about the adverse effect of the agent, and additional studies of pharmacokinetics or pharmacodynamics were also performed [8]. In many cases, phase II clinical trials are well managed and carefully monitored [3]. Phase II security data (including incident reports) is also recorded. If phase II data show that, the drug to be chosen improves the patient's condition and no negative safety considerations emerge. The selected drug will be sent to the final phase of the phase III enrollment study [10]. Volunteers used in phase II courses have 100 numbers per number. The drug will be given to volunteers with an infectious disease. Phase II clinical trials are important in determining drug costs, and Phase II is a poor predictor of drug success [11]. Phase II marks the first drug trial in real patients, and most studies have largely failed in 50,200 patients. Determining the total dose (s) of a given person is one of the criteria for phase II testing [12]. Phase II can be divided into phase II (a), which are clinical trial studies to assess the safety and effectiveness of selected individuals with a disease to be treated or a disease or disease to be diagnosed. Phase II (b) which is a very difficult study. Demonstration of efficacy The development process often fails in phase II where a drug is found to be ineffective or has toxic effects [13].**Phase III clinical trial (Final Assurance of Safety and Performance):**

Typically, 100 to 1000 volunteers, with a drug-induced disease that participated in the phase III study. If Phase II confirms the effectiveness of a given drug. The FDA and sponsors will discuss how to conduct major studies in Phase II and III to learn more about the drug profile in terms of safety and efficacy in different people and to study different doses using a combination of different drugs [13]. Phase III (a) clinical trials are conducted after demonstrating the effectiveness of the drug and before the introduction of the New drug Application (NDA) [14]. Chronic diseases and time trials can be used in practice to study phase III studies [11]. The information collected during the study is used for submission to authorize sales to the sponsor [15,16].

Phase IV Examination (Post-Marketing Studies):

The Phase IV trial is also called "medical use" or "post-market research," FDA-based drug research. Following drug approval the FDA requires a sponsor to conduct a phase IV study [17]. These phase IV studies include "all studies (excluding standard follow-up) conducted after drug approval and related to the accreditation index" [18]. New clinical indications for the drug can be obtained and many patients and clinicians are affected. In Section IV, there is a good chance that we will discuss “all studies that are done after drug approval and related to the approved index”. The Phase IV study is also known as postoperative research. Drug trafficking or surveillance research to confirm the long-term efficacy of a diagnostic drug, vaccine, device, or trial [19]. Phase IV clinical trials include pharmacovigilance safety monitoring and ongoing technical support of the drug after obtaining a commercial control permit. Phase IV courses may be required by regulatory authorities or requested by a sponsoring company for competition or drug interactions or racial tolerance for any reason such as a drug is not certified by the suitability of the reproductive system etc. [20,21].

Post Marketing Marketing Strategies

1. Automatic Reports or Voluntary Reporting:

Most of the side effects of drugs are a project of real-life monitoring or patient reporting. The World Health Organization and the USFDA have used systematic methods to release automated system information, nationally (low, medium or high), national PV systems investing heavily in automated (or voluntary) supply where adverse drug reactions (ADRs) are reported. at a national communication center by health workers, manufacturers or patients directly. From all drug safety monitoring sources, automated media systems provide the best amount of data at rock bottom care costs and set their value at the time of early detection of patient safety questions linked to the product itself or its use. [22].

Table 1: Spontaneous reports or voluntary Reporting Methods

Sources	Experimental strategies	Statistical methodologies	Strengths	Weakness
Spontaneous report	Passive reporting system	Proportional reporting ratio	Huge number to measure the rare adverse events	Confusing by indication
	Active reporting system	Bayesian neural network		Systematic under writing
		Empirical bayes screening		Questionable representative
		Muliti-item gamma poison shrinker		Publicity bias
		Cumulative sum		Extreme duplication
		Random-effects poison regression		Unknown populationat risk

1.1 Rated reporting rating:

Proportional reporting ratio (PRR) is the softest process in the signal acquisition market. A limited number of selected EE reports for all AEs to worry about the selected drug is that a large number of single AE reports of unlimited performance of that drug is thus reduced. sensitivity to other symptoms associated with those drugs PRRs have a large number of positive false positives due to their inaccuracies in many comparisons. [23].

1.2 Bayesian neural network:

The Bayesian neural network is a signal detection method used by a global health organization, which is the most widely analyzed automated reporting system website. Bayesian Neutral Network (BNN) has developed a Bayesian Confidence Propagation Neutral (BCPNN) network, which can handle additional data sets. It is based on the symptomatic relationship between the drug and the side effects. The great advantage of the Bayesian method, is that we are not obliged to guess unknown features, such as the number of degrees of freedom in the model. In the analysis of the Bayesian neural network all values were not confirmed as a possible distribution, and the translation was performed by creating conditional conditions after the intangible variance of interest, given sample observations and previous speculations [24, 25].

1.3 Assessment of Empical bayes:

Calculates the base frequency (expected) below the line (drug) and column (event) independent measurements in multiple two-way tables. If the tree is independent, the equal representation of that drug event should match the appropriate representation of the event on the complete website. Three-dimensional measurements (a) related risk (b) log P (c) geometric definition of the post-distribution relation of the actual related reporting scale was used to measure the frequency of drug events according to its size [3,26].

1.4 Method of sum collected:

The Cum sum method (CUSUM) is predicted as the sum of the differences between your notes and your expected values. Signal is obtained when signal values are above the limit value. Threshold is determined by the average operating time (ARL) based on the definition and variation of the background event. The method requires a certain amount of background pressure and therefore should limit the timely identification of security issues [3,26]

1.5 Poisson Method:

Parameters are measured using high probability, and each AE drug measurement is measured using empirical or parameters or non-parametric parameters in cycles. Confidence intervals (background) that do not involve providing evidence or significant interventions to prevent or correct drug risk [3].

2. Natural methods of unusual event:

Rare cases (e.g., suicidal ideation) occur at prices in the first order of 10,000 or less, and there are a few common drug monitoring options. Another option is to use environmental information that is consistent with changes in prescription drug levels and AE levels. This additional international organization does not support the underlying cause, but the provision of large-scale denominators used and a comprehensive calculation of events such as suicide will reflect thoughtful ideas and simple support drawn from other studies. [3]

Table 2: Ecological methods for rare adverse event

Data source	Experimental strategies	Statistical methodologies	Strengths	Weakness
Ecological methods	National rates	Time series method	Large sample or entire population can be studied.	Do not know if person experiencing the AE actually the drug
	Natural experiment	Change point analyses	Permits between stratum comparisons	Subject to ecological fallacy
	Small area estimation	Mixed effects poison regression	Hypo thesis genre action	Geographic variability in reporting

2.1 Time series method:

The objective of the time series analysis is to define and measure dynamic behaviors that emphasize these observations, to link different observations and to provide suggestions on the origin of the events obtained. Also important features of timeline are whether the measurement is taken equally or not [27].

The Cum sum method (CUSUM) is predicted as the sum of the differences between your notes and your expected values. The signal is received when the signal value exceeds the maximum value. Threshold is determined by the average operating time (ARL) based on the definition and variation of the background event. The method requires a certain amount of back pressure and therefore should limit the timely identification of safety issues [3,26]

2.2 Change the analysis of points:

Finding a change location to identify sudden differences between behaviors due to space or structural changes, while the trend is set as a measure of a gradual departure from the previous process. The point of change can be defined as unpredictability, formation, change in mathematical aspects of various languages**.**

2.3 Combined effect of poisson regression:

One way to calculate heterogeneity while the result of interaction across all routes is a mixed reversal - effects. The measurement process, the probability of the possibility of marginal maximum (MML), is used in a somewhat complex way; however, many standard statistical packages are available on the market to perform this type of analysis. [3].

3. Meta Analysis Method:

Meta-analysis, analysis of the number 2 or more independent studies with the aim of determining the overall outcome and explaining the reasons for variability in the study results, is another potential tool for diagnosing ADRs and assessing drug safety [28].

The main objectives of meta-analysis strategies include the establishment of relationships between drugs and adverse events, the frequency of ADR frequency, and the identification of subgroups with an increased risk of ADR. Meta-analyzes were used to increase statistical power to compare results or test results in small groups. Therefore, it is reasonable to believe that these therapies may also be useful in evaluating drug use and adverse events where each test may not be large enough to show a clear correlation or to measure relationships with increasing accuracy [29].

Table 3: Meta-analysis method

Data source	Experimental methodologies	Statistical methodologies	Strengths	Weakness
Meta-analysis	Synthesis of randomized controlled trials	Fixed effect model	Randomization	Limited generalize ability
	Synthesis of observational studies	Random effect model	Person level	Exclusion of 0 event studies
		Mixed effect logistic regression		Heterogeneity
		Multilevel mixture model		Publication Bias

3.1 Fixed outcome model:

The Mantel-Haenszel (MH) method takes a fixed impact and integrates studies using contrasting statistical variables in the study to determine the load assigned to each study. The basic model of statistical outcomes

included the calculation of the treatment effect rate across all relevant subjects. MH tends to assume that the percentage rate is the same in all subjects [3].

3.2 Random impact model:

The random output model is a strategy model where the total number of parameters representing the components of the model structure reflects the random variance. Standing models define indefinitely the flexibility of the acquisition of harmony between the formal alignment of a building component. The primary goal of a random outcome model is to analyze and measure the total and variance of the number of people drawing the result size. [30].

3.3 Reduction of mixed effect:

Another way to calculate heterogeneity while combining results across all is to evaluate the reversal of the mixed effect. The mathematical features of measuring treatment effect and between the variability of the study using this method are well established.

3.4 Meta-analysis of multi-level mix:

Among other effects a combination of definitions of a random outcome may be harmful in some cases and benefit in another context or alter overtime.

4. Medical claim data:

This simply sets the electronic records of the millions of reported activities between patient providers and health care providers. Hundreds of medical studies published over the past 25 years rely on claims data. The limited use of medical claim data is like replacing the information contained in a patient's medical record [31].

Table 4: Medical claim data tools

Data source	Experimental strategies	Statistical methodologies	Strengths	Weakness
Medical claim data	Case control studies	Fixed effect logistic and poisson	Large samples	Confounding by indication
	Cohort studies	Mixed effect logistic and poisson	Person level	Confounding by time of treatment

4.1 Adjusted logistic and Poisson effect:

We may tend to introduce a 0-point poisson model with a positive effect on each of its scales to determine the response to a health-related factor related to the need for health care. This is usually a dynamic model system that displays statistical estimates of health care usage and data panel account structure [32].

4.2 Mixed outcome planning:

Combined effect reduction is used in the dynamic simulation of binary results, where the inclusion of the result log models as a linear combination of predictable variables in which information is combined or individual combined and random results [33].

Conclusion:

Post marketing surveillance is widely defined as any data collection activity that is carried out close to product authorization. Post-sales surveillance is the practice of testing a drug that works in the market. Vaccines and other medical products have a potential risk factor that has never been heard of. Post-marketing surveillance uses a variety of licensed drug safety monitoring systems, as well as automated data reporting bases, patient registration registers and recording links between health information. Each method is similar to its strengths and weaknesses and is due to the consensus of finding that logical distortions can be drawn. The IV phase trial evaluating drug safety in clinical trials was directed at small tests that may not be strong enough to detect the adverse effect of sufficient sample size should be emphasized in the phase IV trial where safety monitoring is a key activity.

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