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Are view on Phase IV Clinical Trail (Pharma covigilance)

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ABSTRACT

A phase IV clinical trial is an important step in the surveillance of a new drug after its approval for release on the market. It is an essential part of post-marketing research that focuses on real world effectiveness and pharmacovigilance, thus not only continuing previous studies, but complementing them. Phase IV clinical trials differ significantly in their study design, their requirements, and their scientific demand from previous study phases. Phases I to III mainly examine the safety profile of the drug on a smaller scale, as well as the drug's efficacy in a controlled environment of an RCT. Contrarily, phase IV studies claim to uncover even rarer ADRs that could have been overlooked in previous studies and also inspect whether the new drug proves its worth on the free market, in interaction with other drugs and in population groups that had not been previously admitted to the study. The fundamental aim of this article is to conclude phase IV clinical trials in conjunction with the previous preclinical trials to get a bigger picture of the long path. A drug should not be administered until its release in the market . Other goals are to show the relation with different parts of post-marketing research, to investigate the modern role of phase IV studies, and to research the extent to which the current status of phase IV clinical trials meets requirements.

I. 1.INTRODUCTION

Adverse drug reaction (ADR) is a big health concern, in the developed countries. Although rigorous pre-marketing studies are required and performed for all new drugs, the safety profile of a drug at the time of regulatory approval is often incomplete due to some characteristics of phase I– III trials, such as limited sample sizes, short duration of studies, and strict inclusion/exclusion criteria. There are usually important health issues that need to be solved at the time a product is licensed. That is shown by the fact that approximately 20% of drugs acquire new black box warnings in the post-marketing phase, and 4% of the drugs ultimately become withdrawn for safety reasons. Phase IV clinical trials have not been an integral part of the drug development process for very long yet. The regulation for phase IV trials, as we know it today, began in the United States in the year of 1997, as the FDA required annual reporting via post-marketing commitment in the FDA Modernization Act. Since 2007, in the United States, the Food and Drug Administration (FDA) has been authorized by the Food and Drug Administration Amendment Act (FDAAA) to require post-marketing clinical trials to address safety concerns regarding a given drug. In 2009, one billion dollars has been provided by the American Recovery and Reinvestment Act to studies that analyze and compare the effectiveness of new treatments. This shows a rebalancing of the weighting between pre-marketing and post-marketing studies, as the importance of post-marketing surveillance is perceived by both politics and society.(1)(2)

1.GUIDELINE FOR POST MARKETING SURVEILLANCE OF MEDICINES

This guidelines provides information for NMRA to begin executing post-marketing surveillance as a core regulatory function**.**

1. To detect and report any spurious/falsely labelled/falsified/ counterfeit products penetrate to the market and what may be the health impact for patients.
2. To identify SF medical products that have reached consumers and to evaluate pharmacovigilance reporting by healthcare professionals and patients.
3. For raising awareness concerning the importance of reporting an unusual lack of efficacy of medical products
4. To improve and enhance safety measures, which involve statistical analysis of adverse drug reactions (ADRs) as reported by healthcare institutions and patients, thereby

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detecting signals of ADRs that may warrant further investigation.(3)17)

i) Procedure for Post-Marketing Surveillance

- Sampling plan is prepared according to the requirements of NMRA.
- Initial planning under the NMRA is coordinated with other stakeholders.
- NMRA Officers/Authorized Officers carry out sampling according to an established and approved plan.
- NMQAL and other selected laboratories whenever requires carry out tests according to regulations and guidelines (pharmacopeial methods or official verified/validated test methods in product dossiers,).
- Data are analyzed by the NMQAL and reported to the NMRA which is responsible for sharing with all relevant stakeholders.
- NMQAL and enforcement divisions carry out follow-up actions as appropriate.
- Reporting of suspected ADRs to Safety and Risk Evaluation Committee (SAFREC) and evaluation and monitoring safety of reported suspected ADRs.
- NMRA conduct workshops relevant post market surveillance activities to Stakeholders.(7)(9)

2.INFORMATION NEEDED FOR RISK BASED SAMPLING AND TESTING

❖ **Selection of area to Sample**-

Administrative and health structure, updated demographic information, disease prevalence, medicines supply chain, pharmaceutical sector information (number of outlets for each sector).

❖ **Selection of medicines**-

Most-used medicines according to the essential medicines list, complaint investigations, quality failures, most-sold medicines, higher risk medicines (stability, storage) , medicines imported from countries with stringent regulations, supply system of targeted medicine, known points of distribution

❖ **Selection of collection sites**

Complete and up-to date information about the pharmaceutical sector in the area (number of outlets, levels of distribution, type of outlets, type of available sectors for supplies, geographical and administrative structure (e.g., number of provinces, number of districts), demographic information Government health institutions e.g. Guideline for Post marketing surveillance of Medicines government hospitals, medical supplies division (MSD), regional medical supplies divisions (RMSDs), etc and private sector institutions (e.g. wholesale pharmacies and drug stores, community/retail pharmacies, pharmacies and dispensaries at private hospitals). Based on the objectives and testing methodology of the activity, data on the specifications for the medicine and its dosage form are required and should be available at the NMRA. The number of samples is determined based on the objectives and availability at the collection site.

❖ **Sample testing**-

Test to be applied or selected must be determined by NMQAL based on objectives of the sampling and testing activity according to the pharmacopoeial specifications or manufacturers specifications. Manufacturer's/Market authorization holders should provide necessary information related to the quality of their products.

❖ **Handling, storage, and transportation of samples**-

NMRA officers, other relevant authorized officers and healthcare institutions who involve in sending samples to laboratory should observe the following best practices throughout the chain of custody of the products**:**

- Avoid excessive mechanical vibration during transportation.
- Store in original container, where available, and label accordingly.
- Store away from sunlight and excessive humidity.

Collect all the information required for each sample with the location of collection number of samples collected, name of the sample and any observation at the time of collection in the sample collection form – GN-PR-01-F02. Product complaints should be submitted with the form-Submission of Products complaints to NMQAL-GN-PR-01-F03.

- Both forms are posted in the NMRA website. NMQAL Officers who involve in sample collection should use the Government Surveillance Sample Collection form-GN-PR-01-F01.
- Samples that are light or heat sensitive may require special handling, transportation, and storage conditions. If cold storage is indicated, store in an appropriate container and monitor the temperature during transportation.

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- In the case that collectors are not transporting samples directly to the laboratory, samples with the accompanying documents should be sent by a courier service with required storage conditions. For each shipment it should be clearly indicated that samples are sent for laboratory testing purposes only, will not be used on humans or animals, have no commercial value and will not be placed on the market. (4,16)

3.ADVERSE EVENTS OF MEDICINES

- In active post-marketing surveillance programs drug adverse events monitoring is also essential. When a new drug (NCE) is first marketed, it would have been tested only in a limited number of patients. Rare adverse drug reactions could be identified only after the drug is marketed and used by a much larger population. Safety information in use in special groups such as children, elderly, pregnant women etc. are not often available at the time of first marketing of a new drug.
- Healthcare professional such as doctors, dentists, pharmacists and nurses are encouraged to report suspected adverse events encountered in their day to day practice.Adverse drug events can be reported to the NMRA by completing the relevant forms available in NMRA website. The NMRA database for adverse event reporting is a computerized information database designed to support the NMRA's post-marketing safety surveillance.
- The ultimate goal of this system is to improve the public health by providing the best available tools for storing and analyzing safety reports.
- These reports are evaluated by the Safety and Risk Evaluation Sub-Committee (SAFREC)
- As a result, the NMRA may take regulatory actions to improve product safety and protect the public health, such as updating a product's labeling information, or re-evaluating an approval decision and also product recall. For further details refer the guideline for Adverse Reaction monitoring(7,8)

i)NEED OF POST-MARKETING SURVEILLANCE

1) Adverse reactions that occur in fewer than 1 in 3,000 – 5,000 patients are unlikely to be detected in Phase I – III investigational clinical trials, and may be unknown at the time a drug is approved. These rare adverse reactions are more likely to be detected when large numbers of patients are exposed to a drug after it has been approved and marketed.
2) Safety monitoring, nevertheless, is just one form of Post PMS. Another is the planned collection of clinical data relating to the use of a drug through the conduct of PMS studies.
3) These could be general, open studies where unlike premarketing studies, the selection of patients is not strictly defined by stringent inclusion and exclusion criteria, but governed by the permissible indications and contraindications of the drug as stated in the text of prescribing information.
4) This ensures that information is collected in a varied spectrum of patients, and makes it likely that the study will yield data that may not have been captured in Phase III studies. PMS studies exemplify the difference between efficacy and effectiveness.
5) Efficacy is judged within the controlled environment of a clinical trial with strict inclusion and exclusion criteria and close monitoring and ensured compliance. Effectiveness is the real test of a drug when it is used in a much larger population, with varied organ system function, concomitant drugs and where monitoring and compliance are not always ensured.
6) In other words, a PMS study is a non-interventional study requested by regulatory authorities to verify the safety, tolerability and effectiveness of a marketed drug in a particular population per the locally approved label. Conducting such general, open-label PMS studies is a regulatory requirement in countries such as Japan and the Philippines.
7) In India, PMS data used to be submitted to the Drugs Controller General of India (DCGI) within 2 years of launch. Now Periodic Safety Update Reports (PSURs) are filed at regular intervals as specified in the revised Schedule Y of the Drugs and Cosmetics Act. Most, other regulatory authorities, however, do not insist on PMS studies.
8) Instead, in countries such as Germany, regulators may require a company to conduct controlled clinical studies under precisely defined enrollment criteria, to investigate specific concerns and gather information about the drug under specific conditions of use when there is a suspected problem.

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9) The outcomes of such studies could be signals, pharmacoepidemiological information, need for controlled studies, labelling changes with modified undesirable effects section, indications and dosing schedules, and regulatory action (boxed warning, risk minimization action plan, withdrawal).
10) Other phase IV studies could be RCTs, in vitro studies, outcomes research (burden of illness) and pharmacoeconomic studies, drug utilization studies, practical clinical trials, and investigator-initiated research in practice.(6,7)

ii) WHY POST-MARKETING SURVEILLANCE STUDIES ARE NECESSARY?

"Not all Phase IV studies are Post-marketing surveillance studies, but all PMS is a phase IV study".

I. The main focus of this kind of study is to find adverse drug reactions and to guarantee proper safety monitoring of the drug after it is released on the market.
II. It is an adjuvant to spontaneous monitoring systems and has the purpose to detect background signals, which might indicate that there is an issue. There is a transition from the regulatory agencies taking reactive approaches towards more proactive approaches, focusing on prevention.
III. There was a big change in the last few years, as regulatory authorities realized that they have to apply measures to suppress the incidences of adverse drug reactions of novel drugs.
- Examples for this can be found in Canada and the UK. In 2013, in the United Kingdom, around 150 of 100,000 people reported an adverse drug event. Similar were numbers in Canada, where up to 22,000 deaths as a result to novel drugs have been reported each year.

IV. It is expected that the number of reported ADR accounts for only 10% of ADR, and the rest is going unnoticed by regulatory agencies. By implementation of better post-marketing surveillance standards, there should be a better overview of the actual scope of the extent of ADR.
V. The study design of PMSS could be general, open studies with less strict regulation of exclusion criteria than pre-marketing studies, but still follow the exact indication and contraindication criteria that the drug is affirmed to.
VI. The purpose of wider criteria is to allow the study to capture effects of the drug that may have been previously hidden in phases I-III.
VII. In certain countries, those types of studies are required for every drug that is released on the market, such as in Japan.
VIII. In the United States, Periodic Safety Update Reports (PSUR) must be delivered in a predetermined interval to regulatory agencies. PSUR by law requires pharmaceutical companies to evaluate reports of side effects collected from all over the world and to check whether that results in necessity for further restrictions on use or additional side effects have to be taken into account.
IX. Nevertheless, in most countries, like in Germany, the state does not insist companies conduct post-marketing surveillance studies as a requirement for every drug.(8,11)

4.Large Simple Trials

- This kind of trial design is a mixture of a randomized clinical trial and an observational study. LST are useful to identify small or modest effect of a drug, that becomes relevant when noticed in a larger population with a certain common disease or condition. LSTs have a relatively large sample size, compared to RCT of phase I-III, and enough statistical power to detect minor treatment effects.
- Another advantage of LST is that, due to the large sample size, the effects of random error can be minimized. Nevertheless, LST are rarely used as phase IV study design, due to obstacles in implementing LSTs for regulatory purposes. Regulators have made enormous progress in the implementation of large simple trials. The FDA issued a guidance in 2012 on "Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Post approval Clinical Investigations," in order to help trial sponsors determine the amount and types of safety data that should be collected.
- The aim of this was to increase quality of safety assessment without undermining integrity and validity of trial results and decrease the burden on researchers and patients participating in a study, as well as to lower

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trial costs by facilitating the increased use of large, simple trials. A meta-analysis done by Smith et. al, which compared PROBE trials (Prospective, Randomized, Open-Label, Blinded Endpoint) design, which is a variant of LST, with double blind trials in hypertension, showed that both study designs can be statistically equivalent(8)(9).

5.**Randomized Clinical Trial**

- Similar to the study design in the previous phases, a phase IV study can be designed in a randomized clinical trial, with blinded or double-blinded study groups, a placebo group, or a comparator drug to ensure that the participants get their necessary treatment.
- These designs share a very similar structure and methodology like the previous phase III studies. Those trials try to evaluate further the drug's efficacy in a controlled environment and can be seen as an extension of the previous clinical trials. However, as it is stated in Farahani's article, "Clinical data gap between phase III clinical trials (pre-marketing) and phase IV (post-marketing) studies: evaluation of etanercept in rheumatoid arthritis," there are key differences between phase III clinical trials and phase IV post-marketing studies that involve patient characteristics, the clinical setting (environment), and the manner of drug use.
- They found that the rheumatoid arthritis drug profile was different between the patients receiving etanercept in the phase IV community cohort study and the patients enrolled in the RCTs.
- As phase III studies take place in a heavily regulated environment, compared to phase IV studies, there will be always a gap between the results of both, even if they are designed similarly, as phase III is more concerned with efficacy of the drug, whereas in phase IV, the drug is tested for its real-world effectiveness.
- In contrast to pre-marketing phases, phase IV clinical trials, instead of the conventional Randomized Clinical Trial (RCT), can use a more modern approach of the adaptive trial design, which has the goal to increase the flexibility.
- The main issue with widespread use of adaptive clinical trials in the setting of phase IV clinical trials is that the adaptive study design could undermine its validity and integrity(13) (14)

6.Physician Experience Studies

- As the name implies, those are types of studies based on physician reports and therefore often criticized for a lack of scientific accuracy.
- The benefit of this kind of study design is that it is relatively cheap, compared with large and complex RCT, they help physicians gain experience with the new intervention, and they provide information from a big heterogenous pool of population that helps to assess the real-world effectivity and safety profile of the drug.
- An example for this kind of study was the article, "Antihypertensive safety and efficacy and physician and patient satisfaction: results from a phase 4 practice-based clinical experience trial with diltiazem LA," done by Glasser. The study was performed as a large-scale, open label study with more than 15,000 physicians and 130,000 patients enrolled. The results showed that DLA was safe and produced clinically meaningful reductions in blood pressure, as well as a high degree of physician and patient satisfaction(17)(18)

II. CONCLUSION

The phase 4 trial is also referred to as post marketing surveillance and as the name suggests, it is conducted after the drug is already marketed and available to the general public. The main objective of the phase 4 trial is to check the drug's performance in real life scenarios, to study the long-term risks and benefits of using the drug and to discover any rare side effects.

In a phase 4 trial, any rare or long-term effects of the drug can be observed in a much larger population of patients and over a much longer period of time. If safety surveillance does indeed reveal concerns about the drug, it may be withdrawn from the market and no longer made available on prescription.

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