Late Phase Studies:  
The Possible Revolutionary trails

The current late phase market in India is close to 60 million US Dollars which accounts for about 15 % of the total clinical research market. At present phase IV and Post Marketing Surveillance (PMS) studies mainly contribute to the late phase market in India. PMS market is likely to grow faster as DCGI is insisting to do PMS studies on new drugs, new biologics and follow-on biologics/biosimilars before or after launching in India. As health insurance is gaining wide acceptance, cost effectiveness and quality of life assessment studies like outcomes research is the new area which would gain momentum in few years.

Phase I studies are conducted to assess the safety and tolerability of a drug which can take several months and involves a small number of healthy volunteers (20 to 100). Phase II studies test the efficacy and further safety of a drug which can last from several months to two years and involves up to several hundred patients. Phase III Clinical trials conducted after efficacy of the drug is demonstrated, but prior to regulatory submission of an NDA which can last from several months to several years and involves several hundred to several thousand patients. Phase III B Clinical trials are conducted after regulatory submission of an NDA, but prior to the drug approval and launch.

Phase III B and Post marketing trials are considered as late phase clinical studies which are conducted to establish long-term safety and efficacy of a drug in real-world conditions over an extended period of time. Most of the clinical trials and post marketing drug safety data is collected from subjects who have been exposed to the drug for few years. But some health risks may not be identified unless a person has been exposed to a substance for 5, 10, 15 or more years. For example a chain smoker will not develop lung cancer until they have smoked for at least 25 years. So late phase studies are conducted to monitor a drug’s long-term effectiveness and impact on a patient’s quality of life over an extended period of time.

Early phase studies specifically address drug safety and efficacy but they do not detect unforeseen risks of a drug. Example: Nimesulide is a good example. It is an orally administered non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic effect . Nimesulide was first launched in Italy in 1985, since then it has been aggressively marketed in about 50 countries throughout the world. Safety data from clinical trials proven Nimesulide as a preferential COX-2 inhibitor and therefore, assumed to be safer in clinical use but selective inhibition of COX-2 effect on the GI tract was detected only after various epidemiological studies

Late phase studies provide valuable ongoing safety information for risk management through long-term tracking of patients in a real-world clinical setting. Additionally, these studies can target particular therapeutic areas or specific populations where relevant clinical data are required to ascertain the effectiveness and utilization patterns of some product.

The information gained from such studies helps in bringing out the long-term risks of drugs which can play an important role in health promotion and disease prevention. The global regulatory bodies could use this data from long-term drug studies to make required changes in labeling and medication guidance.

Late-phase studies correlate the drug with real life scenarios. For example - In a real-world setting, patients may take several therapies (Polyphramacy) for different diseases. So in addition to controlled pre-marketing clinical trials, it is important to monitor the safety profile of a new drug once it is widely available. This study will also solve the food drug interactions and drug-drug interactions due to Polypharmacy.

Late phase illustrates the difference between efficacy and effectiveness. Example: Minoxidil was first used exclusively as an oral drug to treat high blood pressure. However long term studies shown its side effects as increasing growth or darkening of fine body hairs. From this result a topical solution that contained 2% minoxidil was produced to treat baldness and hair loss.
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. It is a non interventional study requested by regulatory authorities to vary the safety, tolerability, and effectiveness of a marketed drug in a particular population as per the locally approved label. In India, if DCGI suggests, PMS data should be submitted to the DCGI within 2 years of product launch.

Goals of Late phase studies:

- Supports & strengthens the product safety profile and provides a supportive environment for treating physicians.
- Provides “real-world” clinical, economic, humanistic outcomes.
- Demonstrates a commitment to:
  - Patient care
  - Quality improvement
  - Education of healthcare providers
- Influences market expansion & product penetration.
- Identifies factors impacting prescribing decisions.
- Identifies issues related to product use.
- Assesses a known serious risk related to the use of the drug.
- Assesses signals of serious risk related to the use of the drug.
- Assess simultaneously beneficial and adverse responses that could form the basis for cost-benefit analysis.
- Identifies an unexpected serious risk when available data indicates the potential for a serious risk.
- Discovers the unknown side-effects during marketing, including those that may subsequently lead to new indications for drug use.
- The quantitative evaluation of the risks of known adverse effects, whether discovered before or after marketing.

Types of Late Phase Studies:

- Phase III b Studies
- Phase IV Studies
- Registry Studies
- Pharmacoepidemiologic Studies
- Health Economics/Outcomes Research Studies

Phase IIIIB Studies:

Phase III B studies are conducted after regulatory submission of an NDA, but prior to the drug’s approval and launch.

It is a common practice that certain Phase III B trials will continue while the regulatory submission is pending at some regulatory agency. The reasons for performing trials at this stage include attempts by the sponsor at "label expansion" (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing), to obtain additional safety data, or to support marketing claims for the drug.
Phase III trials are not required in all cases, it is typically expected when a regulatory agency considered that a product can be brought to market even though some information is missing from the paperwork, a conditional approval is given along with a request for additional data on the use of a drug.

These Phase III trials are conducted: Specifically to develop additional data in specific sub populations (children, pregnant women and the elderly), to identify less common adverse reactions, to refine dosing recommendations and to compare new product to market-leader standard product.

**Phase IV Studies:**

Phase IV trials involve the safety surveillance (Pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to certain uses.

These are conducted in order to confirm the ADRs and to determine their true incidence, when there are suspected or known adverse drug reactions (ADRs) associated with the drug. Example when a drug belongs to a class of drugs known to be associated with a serious ADR, but its incidence may not be high enough to observe in the limited number of patients in phase III studies. These studies evaluate different formulations, dosages, durations of treatment, drug interactions, and other drug comparisons.

**Post Marketing Surveillance Studies:**

The PMS is primarily designed to allow physicians “to participate in appropriately designed surveillance studies (PMS studies)”, the purpose of which is “to monitor the performance of the medicament under conditions of actual use.”

Pharmaceutical companies/CRO’s, in most cases, actively recruit patients and physicians in the PMS studies in order to expedite the data collection. Physicians enroll their patients whereby product samples may be provided for patients’ use, whether for full course of therapy or as starter dose. Physicians fill out a CRF that has been approved by IEC for PMS purposes and these are routinely collected by the drug company/CRO. Laboratory examinations may be conducted to complete the CRF depending on the requirement of the PMS study.

This study will help the Physicians to collect adverse events in a real world scenario, which were not reported during the clinical trials and which also would decide the Risk/Benefit ratio.

**Registry Studies:**

Registry is an organized system for the collection, storage, retrieval, analysis and dissemination of information on individual persons exposed to a specific medical intervention who have a particular disease, a condition (risk factor) that predisposes them to occurrence of health related event, or prior exposure to circumstances known or suspected to cause adverse health effects.

Through the creation of registries, a sponsor can evaluate safety signals identified from spontaneous case reports, literature reports, or other sources, and evaluate factors that affect the risk of adverse outcomes, such as dose, timing of exposure, or patient characteristics.

Registries collect data on a wide population (with few exclusion criteria) and evaluate care as it is actually provided. Follow-up could be retrospective, prospective, or a combination of both. As a result, registry data are more representative of the real-world patient experience.
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Registries can be particularly useful for:

1. Collecting outcome information not available in large automated databases.
2. Collecting information from multiple sources (e.g., physician records, hospital summaries, pathology reports, vital statistics), particularly when patients receive care from multiple providers over a period of time.

Types of Registry Studies

- Disease registries
- Drug registries

Disease registries collect data on drug exposure and other factors associated with a clinical condition by collecting information using standardized questionnaires in a prospective fashion.
Examples: registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations.

Drug registries collect data of populations exposed to drugs of interest by collecting information using standardized questionnaires in a prospective fashion.
Example: To determine the impact of biological therapies on rheumatoid arthritis patients, a registry of rheumatoid arthritis patients exposed to biological therapies can be followed over time.

Regulatory Agencies, Pharma research specialists and physicians want evidence on real-world effects of medical products, therapies and services, in more diverse populations to estimate whether these are safe and effective in terms of improving quality. Registries sometimes became mandatory as a condition of approval of a healthcare product, which can also provide a stream of information on disease process and care patterns for abstracts and publications.

Pharmacoepidemiological Studies:

Pharmacoepidemiology is the study of drug use and its effects in a large number of randomly non-selected populations. It is primarily focused on measuring safety in the post-marketing phase.

Pharmacoepidemiological studies provides additional information on available premarketing studies, such as identification of previously unknown adverse and beneficial effects, the effect of drug overdoses, the patterns of drug use (including abuse), and the economic implications of the use of the drug.

Pharmacoepidemiological studies collect data on a wide population (with few exclusion criteria) and evaluate the patient care as it is actually provided. Patient follow-up could be retrospective, prospective, or a combination of both. As a result, the data is more representative of the real-world patient experience. They can also give useful data available when a clinical trial is not feasible for ethical or practical reasons (for example, pregnancy exposures or rare diseases).

Pharmacoepidemiology studies provide a powerful mechanism to explore the drug safety and effectiveness in broad-based populations and can serve as a scientific foundation for outcome research.

In Pharmacoepidemiological studies, individuals are observed or certain outcomes are measured. No attempt is made to affect the outcome. For example, if we want to see if smoking is related to lung cancer, it would not be able to ethically assign people to smoke and not smoke, but rather would observe the prevalence of smokers vs non smokers who develops cancer.

Epidemiological study methods include - Cohort studies, Case control studies, Cross sectional studies.
Cohort studies: a group exposed to a particular factor and another group not exposed to this factor will be followed up over time to determine occurrence of disease. The incidence of disease in the exposed group is compared to the incidence of disease in the unexposed group. The best example is the lead revolution study or the fortification of iodine to help the children brain development.

Case control studies: In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population. The exposure status of the two groups is then compared in the two groups.

Cross sectional: These types of studies are primarily used to gather data for surveys. Data will be collected on a population of patients at a single point in time regardless of exposure or disease status.

Health Economic and Outcome Research Studies:

Health economics is a simple analysis of economical aspects of the health sector, applying the concepts from economical theories. It is not possible to determine the product value only on the basis of efficacy and effectiveness in real-world clinical practice. That is the reason why many stakeholders in the healthcare sector increasingly relying on Health Economics and Outcomes Research (HEOR) information in order to understand the product value and its potential completely.

Economic evaluations can provide “value-for-money” information to those making decisions about the allocation of limited health care resources. In particular, economic evaluations can be used to identify interventions that are worth providing and those that are not. Outcomes Research are interdisciplinary science combining principles of epidemiology, clinical research, health economics, quality of life assessment, and health policy.

Controlled trials simply lead to efficacy, which does not provide sufficient information for which to choose a drug product. Endpoints studied in traditional clinical research include blood pressure, cholesterol level and glucose level. Outcomes research, on the other hand determines effectiveness, which focuses on the effect of therapeutic treatments on endpoints such as survival, quality of life, and satisfaction with care. When Health economic studies are also implemented which includes costs along with controlled trials and outcomes research then ultimately we will get efficiency, which plays a major role.

Conclusion:

Late Phase Studies are an integral component of the commercialization effort for a product because it impacts multiple aspects of ongoing clinical and commercial support. Hence Late-phase studies provide more comprehensive data about overall treatment satisfaction and patient HRQoL (health related quality of life) in real-world settings over an extended period of time to detect any undiscovered effects, positive and negative, that may be associated with a drug which may not be possible in earlier clinical trials.

Pharmaceutical companies need to get to grips with late-phase clinical studies if they are to differentiate their products and build a comprehensive value proposition in an increasingly saturated and payer-dominated marketplace.