Strategical Clinical Trials Towards Personalized Medicine: A Detailed Review

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Abstract
Personalized medicine is the novel highly utilized approach in recent drug development process. This method is implemented widely in the areas such as oncology, hematology etc. The personalized drug development process is also a tricky task which requires in-depth consideration and advanced toxicological screening. RCTs (Randomized Controlled Trials) are the foundation of Evidence-Based Medicine (EBM). They have numerous advantages, but they also have certain disadvantages, as they are based on the norms of Good Clinical Practice (GCP). The rigorous methodology followed in RCTs provides for the avoidance of bias due to confounding factors (through a control group), selection bias (by randomization), and interpretation bias (via randomization) (through double blinding). In this review, we focus on the concept of personalized/precision medicine highlighting the history and the adaptation of traditional clinical trials as strategical to complement the personalized drug development process. Then, we look into the merits and demerits of strategical clinical trials in personalized medicine and give an overview of the future dimensions of these clinical trials in personalized medicine.

Keywords: personalized medicine, precision medicine, cancer, randomized clinical trial, strategical clinical trial, clinical trial

1. INTRODUCTION

The study of genes affects a person's response to drugs in the form of pharmacological and toxicological action. Among the genetic polymorphisms, Single nucleotide polymorphisms (SNPs) are a major source of genetic variation, arising as a consequence of errors in DNA replication. In human beings 99.9 % bases are same. Remaining 0.1 % is what makes a person unique. Having sufficient genetic and metabolic data will allow drugs to be tailored to different patient subgroups. [1]

Personalized medicine also known as precision medicine is the tailoring of medical treatment to individual characteristics such as demographics, patient history, molecular analysis (genetic protein metabolism profile) of each patient's disease or response. [2] It is considered as an extension of traditional approaches to understanding and treating disease.

The use of personalized medicine is categorized into:

I. Predictive medicine

II. Treatment optimization

Predictive medicine identifies the patient's risk of developing disease thereby enabling prevention or treatment. Single or more commonly multiple analysis are used to identify further disposition to disease.

Treatment optimization refers to pharmacogenetics and pharmacogenomics aiming to match best available drug or dose to individual genomic profile. [3]

Example: Warfarin, an anti coagulant with narrow therapeutic window, widely prescribed, shows high inter-patient variability in required doses due to different alleles of genes / enzymes. [4]

Genomic advances have provided a biological explanation for the long-observed variation in clinical course and treatment response. The ability to molecularly characterize human diseases opens up new possibilities for creating more successful drugs as well as identify new problems for making clinical trial design and review. [5,6]

This review gives a detailed insight into the evolution of personalized medicine concept over the centuries. This is followed by an explanation of clinical trial methodologies involved in personalized medicine. The key challenges and opportunities these new trial designs can provide for a more efficient drug development process are discussed in this review article.

2. HISTORY OF PERSONALIZED MEDICINE

The term personalized medicine was coined in the late 1990s, but was not introduced to US Public until about a decade later as Genomics/Personalized Medicine. [7] The detailed timeline of

events in the history of personalized medicine is summarized in table 1.[8]

Table 1. Timeline of events in the history of personalized medicine

1866	Gregor Mendel's discovery of Hereditary traits; Mendel's paper was published; units of inheritance in pairs; equal segregation; independent assortment. These ideas were not recognized for next 34 years.
1869	DNA was identified by Fredrich Miescher as an acidic substance found in cell nuclei. The significance of DNA was not appreciated next 70 years.
1902	Sir Archibald Garrod made the first connection between genetic inheritance and susceptibility to a disease.
1905	The word "genetics" was first coined by William Bateson.
1950	In DNA, there are equal amounts of A and T and equal amounts of C and G, as shown by Erwin Chargaff. The A+T to C+G ratio can differ between organisms.
1952	Bacteriophage labelling experiments by Alfred Hershey and Martha Chase showed that DNA mediates heredity.
1953	Watson and Crick deduced the double helical structure of DNA with antiparallel nucleotide chains and specific base pairing.
1956	The first discovery of genetic basis for selective toxicity was made for the antimalarial drug primaquine.
1966	The genetic code was cracked by number of researchers using RNA homopolymer and heteropolymer experiments as well as tRNA labelling polymers.
1973	Recombinant DNA was first constructed by Cohen and Boyer.
1977	Discovery of cytochrome P450 metabolic enzymes and identified their role in chemically altering drugs. This led to the realization that variation in these enzymes can have a significant influence on the effective dose of a drug.
1986	Polymerase Chain Reaction was developed by Kary Mullis.
1994	EGFR TKI class was discovered. Affymetrix introduces the first array of HIV genotyping gene chip.
1996	First cloning of a mammal (Dolly the sheep) is performed by Ian Wilmut and colleagues from the Roslin Institute in Scotland.
1998	Trastuzumab receives FDA approval for metastatic breast cancer with HER2 overexpression.
2001	The sequence of the human genome was released and the "post genomic era" officially begins.
2004	EGFR TKI became an accepted therapeutic option in advanced non -small cell lung cancer. Targeted therapies were approved in colorectal cancer (KARS M+) and non-small cell lung cancer.
2007	Elzentry (R)(maraviroc) a personalized medicine developed by Pfizer and targeted for treatment of a specific strain of HIV known as "CCR5- tropic", was approved.
2011	Zelboraf, a prescription personalized medicine from Genentech, was made available for people with skin cancer melanoma with mutation in BARF gene.
2012	Xalkori, a prescription medicine was released by Pfizer for treatment of non -small cell lung cancer caused by a defect in ALK (anaplastic lymphoma kinase) gene.

3. CLINICAL TRIAL METHODOLOGIES INVOLVED IN PRECISION MEDICINE

Precision medicine, according to the National Institutes of Health, is an "emerging method for disease treatment and prevention that recognizes heterogeneity in genes, climate, and lifestyle for each person."[9] Dr. John Danaher, president of Elsevier Clinical Solutions, expands on this concept by mentioning the functional aspects of precision medicine, such as collecting patient data — genomic and otherwise from EMRs, EHRs, and imaging devices to more accurately address clinical questions. [10] For most illnesses, precision medicine isn't the practice. However, these cutting-edge therapies are now assisting in the treatment of disorders with a clear genetic correlation, such as epilepsy, cystic fibrosis, and some cancers. One-person trials, also known as "n of 1 trials," are now taking place, as well as a small number of larger clinical trials. [11]

Another new type of trial spawned by the search for precision therapies is the National Cancer Institute's MATCH project. It will analyze tumor DNA from approximately 6,000 people whose tumors have failed to respond to standard therapies. Those with gene modifications (called "mutations" by doctors) for whom targeted therapies are available will be allocated to those medications in various parts of the body. [12,13]

3.1 Phases of clinical trials

Clinical trials are basically of phases five phases among that only four phases are considered as main phases they are as follows:

Phase 0

The first clinical trials of people are known as phase 0 trials. They want to know how a drug is metabolized and how it affects the body. A very small dose of a drug is given to around 10 to 15 participants in these trials.

Phase 1

Phase I trials are designed to assess the most appropriate dose of a new medication while minimizing side effects. A small group of 15 to 30 patients will be used to assess the drug. Doctors begin by administering very low doses of the medication to a small number of patients. Other patients are given higher doses before side effects become unbearable or the desired result is achieved. Since the medication may benefit patients, Phase I trials are used to assess a drug's safety. If a drug is found to be effective, it can be put to the test.

Phase 2

Phase II trials are used to determine whether or not a medication is safe and effective. Patients with a particular form of cancer are often screened for the drug. In comparison to Phase I trials, Phase II trials include a greater number of patients. New drug formulations are often reviewed. Patients are closely monitored to see if the medication is successful. The new drug, on the other hand, is rarely compared to the latest (standard-of-care) drug. A phase III clinical trial will be used to evaluate a drug if it is found to be effective.

Phase 3

Phase III trials equate a potential medication to the current standard of treatment. These trials analyze each drug's side effects as well as which drug performs better. A total of 100 patients must be enrolled in a Phase III trial.

Phase 4

Phase IV trials are used to evaluate experimental medicines that have been approved by the FDA. The drug is put to the test in tens of thousands of people. This allows for further research into short- and long-term side effects, as well as protection. Any unusual side effects, for example, can only be observed in large numbers of people. Doctors can also learn more about the drug's effectiveness and whether it's beneficial when combined with other medications. [14,15]

The traditional clinical trial designs aren't compatible for personalized medicine development. Industries experience hiccups while performing clinical trials as detailed below.

3.2 Industrial insight on clinical trials

The pharmaceutical and biotechnology industries perform a significant number of clinical trials with the primary aim of discovering new therapeutic agents and gaining FDA approval for clinical use. [16] These research and development activities are extremely expensive (hundreds of millions of dollars) but are essential for cancer care advancement. [17] Publicly sponsored clinical trials are also important in advancing research and patient care, and they supplement industry trials by answering issues that are important to patients but are not likely to be top priorities for industry. [18,19] Companies, for example, will have less incentive to:

- conduct clinical trials to compare the efficacy of various treatment methods that have already been licensed for clinical usage,
- combine innovative therapies established by various sponsors
- create vaccines for rare diseases
- determine the best treatment period and dosage using medications currently in use in clinical trials.
- research screening and preventive approaches,
- special attention to recovery and quality of life after therapy. [20]

To overcome these, it is important to initiate strategical clinical trials towards personalized medicine.

4. HISTORY OF CLINICAL TRIALS IN PERSONALIZED MEDICINE

The history of clinical trials spans a wide spectrum of challenges-scientific, ethical, and regulatory from the first recorded trial of legumes in biblical times to the first randomized control trial of streptomycin in 1946. Most of the elements of a control trial were present in James Lind's famous 1747 scurvy trial. [21,22]

In 1943, the UK Medical Research Council performed the first blind control trial of patulin for the common cold. This paved the way for the Medical Research Council of the United Kingdom to conduct a randomized control of streptomycin in pulmonary tuberculosis in 1946. With systematic enrolment requirements and data collection, this landmark trial was a model of meticulousness in design and execution. with the haphazard quality of another recent research. The streptomycin trial has been referred to as ground breaking over the years as the discipline of control trials has grown in complexity and impact. Several landmarks in human rights ethics have been accomplished – Nuremberg code, declaration of Helsinki Belmont report, and an international conference on harmonization of good clinical practice guidelines in 1996. Clinical studies, like ethical standards, started to be enshrined in law when government officials acknowledged the need to monitor medical treatments in the early twentieth century. If scientific progress continues, new ethical and regulatory problems will arise, necessitating dynamization. [23]

By the twentieth century, physicians had established a personalized approach to medical care. With the rise of blood transfusions, for example, information accrued that showed that people had different blood groups. The fact that such people were grouped together resulted in successful blood transfusions. Doctors later progressed in their documentation of an individual's disease relationship based on their family's "histories."[24] This was achieved in the case of illnesses that tend to be passed down through the centuries.

With the completion of the human genome project in the early twenty-first century, personalized medicine became a bigger impact. This project took an approach that linked people's genetic makeup to their wellbeing. [25] This allowed doctors to perform genetic mapping, which revealed that 99.1% of people's genetic maps are similar. The rest is determined by the differences that exist among humans [26] This explains why different people react differently to different drugs, necessitating drug customization based on individual differences. [27]

4.1 Case studies related to personalized medicine clinical trials

There are over 300,000 registered clinical trials worldwide and approximately 105,000 in the United States. These studies examine whether medications, medical devices, and other treatments (such as using vitamin D for multiple sclerosis) are effective and safe. [28,29] Clinical experiments are carried out on humans. They generally follow successful animal studies. Some of the successful discoveries are mentioned below.

4.1.1 Cancer

Cancer treatment has advanced much with the promise of personalized medicine. Recent scientific advances have shown that there are numerous genetic changes common in cancer types, raising the possibility of developing drugs targeting those dysregulations irrespective of the tumor type. [30,31] Precision Cancer Medication (PCM) was born based on this research gap in which selective tumor targeting agents were employed to minimize the side effects. [32-34] Simultaneously, therapeutic medicine is increasingly expanding, and the number of new drugs (including immune oncology agents) entering drug production is growing. These factors, combined with close cooperation from regulatory agencies, have resulted in the approval of novel agents based on phase 2 results. This will eventually help ensure that PCM becomes a reality for patients. [35-37]

New mechanisms for stronger and faster coordination between all stakeholders in drug development, including academic institutions and frameworks, physicians, pharmaceutical firms, and regulatory agencies, have been developed in tandem with the growing complexity of these clinical trials. [38,39]

4.1.2 Asthma

Asthma is a broad term that encompasses a variety of conditions. In the late 1990s, the idea of separating asthma into various diseases arose. [40,41]The ability to identify subgroups of patients with shared clinical features in order to better understand asthma pathophysiology and improve care led to the identification of asthma phenotypes. [42] The most significant contribution came from the use of statistical algorithms, which replaced clinicians' subjective approach. [43] By objectively grouping patients with similar clinical features into clusters, these multivariate algorithms identified asthma phenotypes. [44] This procedure was used by Haldar et al. on patients with mild to moderate asthma who were being treated in primary care; identified three asthma subtypes. [45] In addition, patients with severe asthma were treated in secondary care. Signs and symptoms like atopic allergy, eosinophilic inflammation, psychological status, and airflow obstruction were the variables used in the algorithm. Other factors included gender, body mass index (BMI), and age of onset of asthma. Patients with high symptom expression, early onset, and minimal eosinophilic inflammation, as well as patients with predominant eosinophilic inflammation, few symptoms, late onset, and male preponderance, were identified as two other subgroups. Depending on the variables used, different sets of phenotypes are specified. In a separate analysis, 34 variables were used in patients with extreme severity asthma. [46,47] There were five patient subgroups identified. The findings were similar to those of the previous analysis, but

due to the larger number of variables used, the subgroup definitions were more precise. Patients in Subgroup 1 were mostly females with early-onset atopic asthma and normal lung function who required minimal medication. Their forced expiratory volume in 1 second (FEV1) was moderately reduced, and oral corticosteroids were frequently used. Airflow obstruction was present in both subgroups 4 and 5. Patients in subgroup 4 were atopic and had developed asthma as an infant. Both sexes were represented equally. Patients in subgroup 5 had a later onset of illness, a female preponderance, and were less atopic than those in subgroup 4. No noticeable changes were observed in other groups. Other studies have corroborated these findings. [48,49] The phenotype of a patient tends to be relatively stable over time. [50] The variables used in cluster analyses must be carefully chosen. Despite the fact that these studies have significantly enhanced our knowledge of asthma, their findings are likely to provide a simplified and accurate view of the disease. Co morbidities and other nuanced factors such as diet and exposure history are currently difficult to integrate into these studies.

Personalized Medicine has made great progress due to the expansion of pharmacogenomics research. The developments of miRNA profiling, epigenetics investigations, metabolites screening and microbiota research will make personalized medicine possible for cancers to common complicated diseases. These developments will revolutionize medical care for patients in near future.

5. ADVANTAGES AND DISADVANTAGES OF STRATEGICAL CLINICAL TRIALS IN PERSONALIZED MEDICINE

Strategical clinical trials in Personalized medicine offers the following merits and demerits (Table 2). [51-53]

Table 2. Advantages and disadvantages of strategical clinical trials in personalized medicine

Advantages	Disadvantages
Opportunity to contribute to advancement of research. Improvement of FDA oversight of test, drugs and other technologies to support innovation while ensuring that products are safe and effective. Doctors can use patients' genetic information as part of routine medical care. Improved approaches to preventing, diagnosing, and treating a wide range of diseases. Customized pharmaceuticals may eliminate life threatening adverse reactions. Reduced costs of clinical trials by, quickly identifying total failures Favorable responses for particular backgrounds. Validation of unique and predictive biomarkers measuring treatment outcomes will need to be in place before medicines developed in this way can be authorized. Product differentiation in the Market place. Preventive Strategies Focused Therapies Higher probability of desired outcome with a drug. Reduced Hospitalization eg: Oncologists in the Netherlands estimate the mean hospital stay for Personalized Medicine is 3-4 days compared to more than a week for Chemotherapy regimens.	Infrastructure requirements: Precision medicine has the potential to have a huge effect on health care, but it will take a lot of money and time to implement. Legal problems: For precision medicine to achieve optimal effectiveness, a significant amount of genomic data from a diverse population must be obtained. if and when such a large volume of data is legally collected. Insurance providers, will not use this knowledge ethically, for example, by refusing to sell certain policies to people with genetic predispositions.

6. REGULATORY OVERSIGHT

In current scenario, various international bodies realized the potential application of personalized medicine in minimizing medication errors and enhancing patient safety profile with high therapeutic outcome. Adhering to this understanding, those international bodies started framing guidelines for real time implementation of personalization to the society. [54-58]

FDA have started developing specific regulatory science standards, research methods, reference material etc. to incorporate personalized medicine into current regulatory policies. It is a challenge for FDA to demonstrate the effectiveness of drug relative to current standard of care. [59,60] The regulatory policies/ guidance document from FDA is summarized in table 3.

Table 3. Regulatory policies / guidance document from FDA

2007	Guidance on Pharmacogenomic Tests and Genetics Tests for Heritable Markers.
2008	E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories.
2012	Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical studies.

	Guidance on Clinical Trial Designs Employing Enrichment Designs.
2013	Guidance on Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase. Clinical Studies and Recommendations for Labeling.

This will help to make precision medicine a reality for many patients by overcoming the existing limitations.

7. FUTURE PERSPECTIVES

Technologies such as high throughput screening, micro fluids and imaging can help to conduct multitude of complex measurement as clinical samples.

7.1.1 Data / technology

In upcoming years, digital technology will influence health and well -being of

citizens. Comprehensive health data will be available through EHR (Electronic health report).

7.1.2 Inter-sectoral synergies

The health care system of future will have evidence based novel personalized medicine treatments. Personalized medicine drives innovation particularly in areas such as digital technology, bio-marker detection, development of molecular targeted drug etc.

7.1.3 Health care system reforms

Economic sustainability and societal benefits of personalized medicine are clear and integrate. In future, adequate reimbursement models supports more equitable approach, consider long term value of innovative technology based approaches.

7.1.4 Education and literacy

Pharmacists, nurses, therapists make the informed, empowered, engaged health care providers of future. They can be provided with health data education and literacy in personalized medicine including ethical, regulatory and data issues. [61,62]

8. CONCLUSION

This literature review provided an inclined view on adapting revised clinical trial towards personalization of medicine. We initially started with data extraction from regulatory journals and clinical trial related publications. With this screened data we initiated a correlation towards personalized medicine and found a lack of regulations specific for personalized medicine clinical trial plan. This gap further provides us with a clue to create a strategic plan as per current guidelines for carrying out personalized medicine clinical trial.

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