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A COMPREHENSIVE REVIEW OF PERSONALIZED MEDICINE CLINICAL TRIALS AND REGULATORY FRAMEWORKS

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ABSTRACT

Personalized Medicine is a revolutionary healthcare approach, tailors medical treatments to individual patients based on their unique characteristics. This article aims to explores the evolving landscape of Personalized Medicine clinical trials, with over 300,000 global clinical trials evaluating drug efficacy, safety, and treatments. Personalized Medicine has gained significant traction, particularly in cancer studies. The global market for Personalized Medicine reached a noteworthy USD 538.93 billion in 2022, with a projected compound annual growth rate (CAGR) of 7.20% from 2020 to 2030. Regulatory directives in the USA and Europe encompass multifaceted processes, including directives of registration process, reflecting the intricate nature of PM regulatory landscapes. In this article it covers compilation of required documents for clinical trials of Personalized medicines for quick referencing in USA & Europe. Personalized Medicine clinical trials hold immense potential for the future of healthcare, as technology advances will further drive the development of tailored treatments. It calls on readers to stay updated with this rapidly evolving field, as personalized medicine promises a brighter and healthier future for patients worldwide.

Keywords: Personalized Medicine, Clinical trial, Study design, Compound annual growth rate (CAGR)

INTRODUCTION

Personalized Medicine (PM) represents a ground breaking approach to healthcare by customizing medical treatments based on the unique characteristics of each patient **[1]**.

Clinical trials in Personalized Medicine aim to adapt medical treatments to an individual's specific genetic makeup, transforming how we approach disease prevention, diagnosis, and treatment. This article delves into the concept of Personalized Medicine clinical trials, exploring their potential advantages, challenges, and future prospects. The United States hosts over the clinical trials, with more than 300,000 conducted globally. These trials evaluate the efficacy and safety of drugs, medical devices, and various treatments **[2]**.

Personalized medicine (PM) is a developing field that seeks to treat patients by offering them tailored therapies based on their individual demographic, genomic, or biological attributes. Many innovative and complex trial designs have been implemented, especially in cancer studies, to evaluate targeted treatments in patients' clusters. However, such trial designs raise concerns about their methodology. Frequently, these trials necessitate separate statistical assessments for each sub-protocol. Interim analyses guide potential adjustments by introducing new interventions or populations, and sub-protocols may be terminated due to issues related to futility or safety.

Personalized Medicines Markets USA

Personalized medicine contributes to the aim of delivering more accurate, anticipatable, and resilient healthcare tailored to individual patients. The size of the worldwide personalized medicine market reached USD 538.93 billion in 2022 and is expected to experience a compound annual growth rate (CAGR) of 7.20% from 2020 to 2030 **[3]**.

The **Personalized Medicine** Market size was valued at USD 538.9 Billion in 2022, expecting a CAGR of 6.9% during the forecast period (2023-2030), and the market is projected to be worth USD 919.03 Billion by 2030.

Table 1: "Personalized Medicine" biomarkers used for therapy of disease [12, 19, 20, & 25]

Drug	Therapeutic area	Biomarker	Referenced subgroup	Efficacy
Abcavir	Infectious disease (HIV)	HLA-B	HLA-B	High risk of immune mediated hypersensitivity reaction & should not receive abcaivar
Afatinib	Oncology	EGFR	EGFR 19 deletion	These mutains incur sensitivity to afatinib tratment
Aripiprazole	Psychiatry	CYP2D6	CYP2D6 poor metabolizers	Half of the usual dose should be administered
Carvedilol	Cardiology	CYP2D6	CYP2D6 poor metabolizers	High plasma concentrations of carvedilol
Clobazam	Neurology	CYP2C19	CYP2C19 poor metabolizers	Avoid clobazam or start with a low dose (2.5mg/Day)
Omeprazole	Gastroenterology	CYP2C19	CYP2C19 poor metabolizers	Lower the dose to avaoid prolonged sedation & unconsciusness

- **Directives of Registration Process (USA) for Personalized Medicine & Personalized Medical Devices [5, 6, 12, 14, 16]**
  - Drug Master File (DMF)
  - Laboratory development tests (LDTs)
  - Modular & Combination products fillings
  - Emergency Use Authorization
  - Investigational New Drug Application
  - New Drug Application
  - Abbreviated New Drug Application
  - De Novo Pathway
  - IDE & IRB submissions (**Personalized Medical Devices**)
  - 510K (Premarket Notification) submission (**Personalized Medical Devices**)
  - Premarket Approval (**Personalized Medical Devices**)
  - Biologics License Application (**Personalized Medical Devices**)
  - CLIA waiver (**Personalized Medical Devices**)
  - QMS certification (**Personalized Medical Devices**)
  - 513(g) request for device classification (**Personalized Medical Devices**)
- **Directives of Registration Process (EUROPE) for Personalized Medicine & Personalized Medical Devices [5, 6, 12, 14, 16]**
  - Active substance master file (ASMF)
  - Centralized Procedure
  - Decentralized Procedure
  - National Procedure
  - CLIA waiver (**Personalized Medical Devices**)
  - CE certification process (**Personalized Medical Devices**)
  - Certificate of Suitability (CES) (**Personalized Medical Devices**)

Table 2: Required documents for Approval Process USA & EUROPE FOR PM[4-8]

Parameters	USA	EUROPE
Regulatory agency	Federal Food & Drug Administration	European Medicine Agency
Application Submission	Application form + Cover letter	Cover letter + EU eCTD envelope
Information Submission	Applicants are required to submit all the information as reports (clinical and non-clinical) for a particular study in modules 4 and 5 in the form of a Study Tagging File (STF) as per the USFDA.	The "EU-envelope" component is created for various submissions (such as MAAs, variations, renewals, etc.) related to a specific medicinal product. It is primarily utilized for the initial, straightforward processing at the Agency level, offering metadata at the eCTD application and sequence levels.
Validity	Every 5 years	5 years for initial MAA
Required documents	Module 1 Module 2 Module 3 Module 4 Module 5	Module 1 Module 2 Module 3 Module 4 Module 5
Assessment	Evaluation of the balance between benefits and risks.	Evaluation of the balance between benefits and risks.

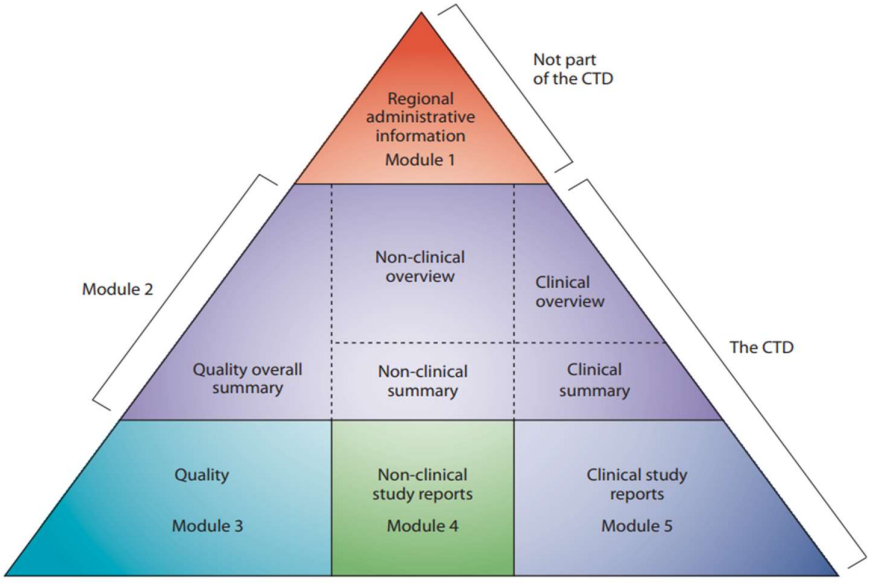
Submission	eCTD (Submission without the inclusion of any physical documents.)	eCTD Submission in both physical (hard copy) and digital (soft copy) formats, with the possibility of providing extra documents on paper being discretionary.
Timelines	120 days (90 days assessment + 30 days clock-stop) - CP 90 days (DCP/MRP)	15 days – 24 months
Mock-ups required	No	Yes

Clinical Trials in Personalized Medicine:

Clinical trials form the backbone of medical research, and Personalized Medicine is no exception. These trials aim to study the effectiveness of tailored treatments and diagnostic tools based on a patient's genetic profile. By enrolling patients with specific genetic markers or mutations, researchers can identify how these individuals respond to various treatments. The outcomes of these trials offer valuable information regarding the efficacy and safety of the interventions personalized treatments, paving the way for their integration into mainstream medical practice.

Data Requirements and Documentation:

The standardized data sets and regulatory requirements for obtaining marketing authorization approval are unified and outlined in the ICH M4 guideline, known as the "Common Technical Document" (CTD) **[31]** along with its electronic version, of eCTD **[32]**. Instructions on the format and details for the clinical overview and clinical summary sections within module 2, as well as the Report of the study within Module 5, are presented in the ICH Topic M 4 E guideline **[32-33]** and its Revisions R1 **[34]** and R2 **[35]**.



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Figure 1: Structuring the common technical document for the purpose of registration [31] (Image Source: https://www.ich.org/page/ctd)

Table 3: Organisation of the common technical document for the registration of PM for human use

Module/Section in CTD	Name of Module/Section
Module 1	**Administrative Information and Prescribing Information**
Section 1.1	Table of Contents
Section 1.2	Documents Specific to Each Region (for example, application prescribing information) forms,
Module 2	**Common Technical Document Summaries**
Section 2.1	Common Technical Document Table of Contents
Section 2.2	CTD Introduction
Section 2.3	Quality Overall Summary
Section 2.4	Nonclinical Overview
Section 2.5	Clinical Overview
Section 2.6	Nonclinical Written and Tabulated Summaries
Section 2.6.1	Pharmacology
Section 2.6.2	Pharmacokinetics
Section 2.6.3	Toxicology
Section 2.7	Clinical Summary
Section 2.7.1	Summary of Biopharmaceutic Studies and Associated Analytical Methods
Section 2.7.1.1	Background and Overview
Section 2.7.1.2	Summary of Results of Individual Studies
Section 2.7.1.3	Comparison and Analyses of Results Across Studies
Section 2.7.1.4	Appendix
Section 2.7.2	Summary of Clinical Pharmacology Studies
Section 2.7.2.1	Background and Overview
Section 2.7.2.2	Summary of Results of Individual Studies
Section 2.7.2.3	Comparison and Analyses of Results Across Studies
Section 2.7.2.4	Special Studies
Section 2.7.2.5	Appendix
Section 2.7.3	Summary of Clinical Efficacy
Section 2.7.3.1	Background and Overview of Clinical Efficacy
Section 2.7.3.2	Summary of Results of Individual Studies
Section 2.7.3.3	Comparison and Analyses of Results Across Studies
Section 2.7.3.4	Analysis of Clinical Information Relevant to Dosing Recommendations
Section 2.7.3.5	Persistence of Efficacy and/or Tolerance Effects
Section 2.7.3.6	Appendix
Section 2.7.4	Summary of Clinical Safety
Section 2.7.4.1	Exposure to the Drug
Section 2.7.4.2	Adverse Events
Section 2.7.4.3	Clinical Laboratory Evaluations
Section 2.7.4.4	Vital Signs, Physical Findings, and Other Observations Related to Safety
Section 2.7.4.5	Safety in Special Groups and Situations
Section 2.7.4.6	Post-marketing Data
Section 2.7.4.7	Appendix
Section 2.7.5	Literature References
Section 2.7.6	Synopses of Individual Studies
Module 3	**Quality**
Section 3.1	Table of Contents
Section 3.2	Body of Data
Section 3.3	Literature References
Module 4	**Nonclinical Study Reports**
Section 4.1	Table of Contents
Section 4.2	Study Reports
Section 4.3	Literature References

TABLE CONTD…..

Module 5	Clinical Study Reports
Section 5.1	Table of Contents of Module 5
Section 5.2	Tabular Listing of All Clinical Studies
Section 5.3	Clinical Study Reports
Section 5.3.1	Reports of Biopharmaceutic Studies
Section 5.3.1.1	Bioavailability (BA) Study Reports
Section 5.3.1.2	Comparative BA and Bioequivalence (BE) Study Reports
Section 5.3.1.3	In vitro-In vivo Correlation Study Reports
Section 5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies
Section 5.3.2	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
Section 5.3.2.1	Plasma Protein Binding Study Reports
Section 5.3.2.2	Reports of Hepatic Metabolism and Drug Interaction Studies
Section 5.3.2.3	Reports of Studies Using Other Human Biomaterials
Section 5.3.3	Reports of Human Pharmacokinetic (PK) Studies
Section 5.3.3.1	Healthy Subject PK and Initial Tolerability Study Reports
Section 5.3.3.2	Patient PK and Initial Tolerability Study Reports
Section 5.3.3.3	Intrinsic Factor PK Study Reports
Section 5.3.3.4	Extrinsic Factor PK Study Reports
Section 5.3.3.5	Population PK Study Reports
Section 5.3.4	Reports of Human Pharmacodynamic (PD) Studies
Section 5.3.4.1	Healthy Subject PD and PK/PD Study Reports
Section 5.3.4.2	Patient PD and PK/PD Study Reports
Section 5.3.5	Reports of Efficacy and Safety Studies
Section 5.3.5.1	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
Section 5.3.5.2	Study Reports of Uncontrolled Clinical Studies
Section 5.3.5.3	Reports of Analyses of Data from More Than One Study
Section 5.3.5.4	Other Clinical Study Reports
Section 5.3.6	Reports of Post-Marketing Experience
Section 5.3.7	Case Report Forms and Individual Patient Listings
Section 5.4	Literature References

Table 4: Phases of Non-Personalized Medicine & Personalized Medicine [4]

Non Personalized Medicine	Personalized Medicine
Phase 0: Discovery/Pre-clinical	**Phase 0: Diagnosis**
Phase 1: First-in-human	**Phase 1: Intervention Point assessment**
Phase 2: Exploratory Trials	**Phase 2: Intervention choice**
Phase 3: Confirmatory Trials	**Phase 3: Intervention Testing**
Phase 4: Post-Marketing Surveilance	**Phase 4: Data warehousing the results**

Table 5: Trial designs implemented to Personalised Medicine (USA & EUROPE) [9-30]

Trial designs	Core Designs
Marker stratified design	Randomise-all
1. Marker-stratified design	
2. Biomarker-stratified design	
3. Stratified-Randomised design	
4. Stratification design	
5. Stratified design	
6. Stratified Analysis design	
7. Marker by treatment – interaction design	
8. Marker-by-treatment interaction design	
9. Treatment by marker interaction design	
10. Treatment-by-marker interaction design	
11. Marker x treatment interaction design	
12. Treatment-marker interaction design	
13. Biomarker-by-treatment interaction design	
14. Non-targeted RCT (stratified by marker) design	
15. Genomic Signature stratified designs	
16. Signature-Stratified design	
17. Randomisation or analysis stratified by biomarker status design	
18. Marker-interaction design	
Hybrid design	Randomise-all
1. Mixture design	
2. Combination of trial designs	
3. Hybrid biomarker design	

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Platform design	
Basket design	
Umbrella design	
Umbrella-basket hybrid	

Biomarker strategy design without biomarker assessment in the control arm	Biomarker-Strategy
1. Biomarker-strategy design with standard control	
2. Direct-predictive biomarker-based	
3. RCT of testing	
4. Test-treatment	
5. Parallel controlled pharmacogenetic diagnostic study	
6. Marker strategy	
7. Marker-based with no randomisation in the non-marker- based arm	
8. Marker-based strategy	
9. Marker strategy design for prognostic biomarkers	

Biomarker strategy design with biomarker assessment in the control arm	Biomarker-Strategy
1. Marker strategy design	
2. Biomarker-strategy design	
3. Strategy design	
4. Marker-based strategy design	
5. Marker-based design	
6. Random disclosure design	
7. Customized strategy design	
8. Parallel controlled pharmacogenetic study design	
9. Marker-based strategy design I	
10. Biomarker-guided design	
11. Biomarker-based assignment of specific drug therapy design	
Biomarker strategy design with treatment randomisation in the control arm	Biomarker-Strategy
1. Biomarker-strategy design with a randomised control	
2. Modified marker-based strategy design (for predictive biomarkers)	
3. Biomarker-strategy design with randomised control	
4. Marker-based design with randomisation in the non-marker-based arm	
5. Marker-strategy design	
6. Augmented strategy design	
7. Trial design allowing the evaluation of both the treatment and the marker effect	
Adaptive parallel Simon two-stage design	Randomise-all
1. Biomarker-adaptive parallel two-stage	
2. Adaptive parallel	
3. Two-parallel Simon	
4. Two-stage design	
Multi-arm multi-stage design	Randomise-all
1. Adaptive biomarker-driven design	
2. Adaptive analysis	
3. Adaptive multi-stage designs	
4. Multi-stage	

Marker stratified design: The marker-by-treatment interaction design uses biomarker status as a stratum (or multiple strata) to investigate the link between the biomarker and the effect of therapy, presuming that the total population can be divided into subgroups based on markers.

Hybrid design: This method assigns patients based only on biomarker positivity at random to either the experimental or control therapy groups, whereas patients based on biomarker negativity receive the control treatment.

Biomarker strategy design with biomarker assessment in the control arm: For trials testing a biomarker's ability to guide treatment choices in oncology, the Biomarker Strategy Design has been recommended. In these trials, patients are randomized at random to receive standard chemotherapy or to be placed in a biomarker-directed treatment arm, in which the treatment strategy is determined based on the patient's biomarker status.

Biomarker strategy design without biomarker assessment in the control arm: Biomarker status is only obtained in patients assigned to the biomarker-strategy arm in situations where it is neither practical or moral to analyze the biomarker in all patients.

Biomarker strategy design with treatment randomisation in the control arm: Using the biomarker-strategy design with treatment randomization in the control treatment, we can ascertain whether the biomarker-based strategy performs better in the general population than both the standard therapy and the experimental treatment.

Sequential Multiple Assignment Randomised Trial (SMART) design: Based on an individual's response, interventions are sequenced using the SMART design. Because of this, the SMART design compares intervention sequences based on how effective each intervention is as well as how the components and duration of the interventions are adjusted. An organized method for evaluating the decision rules governing the order of interventions is offered by SMART designs.

Adaptive parallel Simon two-stage design: The objective of the design is to test a novel treatment that might have a different treatment impact in biomarker-positive subgroups than in biomarker-negative subgroups.

Multi-arm multi-stage design: It can compare many experimental therapies with the standard treatment simultaneously and provide more reliable results more quickly than if separate Phase II trials were carried out to assess each novel treatment separately.

CONCLUSION:

Personalized Medicine (PM) represents a ground breaking paradigm in healthcare, tailoring treatments based on individual characteristics. With over 300,000 global clinical trials evaluating drug efficacy and safety, PM has witnessed significant growth, especially in cancer studies, employing complex trial designs. Despite innovative designs, concerns arise over the methodology of trials, often requiring separate statistical assessments for sub-protocols. Revolutionizing healthcare, personalized medicine customizes treatments for individual patients by considering their unique characteristics. The future of personalized medicine holds immense promise, driven by the integration of emerging technologies that will revolutionize healthcare and transform patient outcomes. With precision therapies, treatments will be precisely tailored to each patient's specific disease characteristics, leading to higher treatment success rates and fewer adverse effects. This framework, gives emerging focuses on clinical trials & developments of improved patient outcomes & also this regulatory framework study that will help others & come out with stringent & systematic guidelines of regulatory landscaps. As technology continues to advance, Personalized Medicine clinical trials hold immense potential for the future of healthcare. The integration of these advancements into clinical practice will lead to a paradigm shift in healthcare, allowing patients to benefit from treatments that address their unique genetic makeup. As Personalized Medicine continues to grow, addressing challenges and embracing innovative trial designs will be essential for advancing personalized healthcare.

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