Adaptive Clinical Trials in Precision Medicine: A Framework for Enhancing Cancer Research and Patient Care

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Abstract

Background: Adaptive clinical trials and precision medicine represent a transformative era in medical research, where innovation and personalized approaches converge. This study examines the intersection of these two methodologies, resulting in a new paradigm for improving patient outcomes. Methods: This paper reviews the dynamic nature of adaptive clinical trials, characterized by their flexibility and responsiveness, and explores their synergy with precision medicine. The focus is on how these trials integrate real-time patient data, enabling rapid modifications to treatment strategies based on individual genetic and molecular profiles. Results: The fusion of adaptive trials and precision medicine creates unprecedented opportunities in medical research. Adaptive trials allow real-time adjustments based on new findings, while precision medicine provides the framework for targeting interventions to specific genetic signatures, enhancing treatment efficacy. Conclusion: The integration of adaptive clinical trials with precision medicine offers a new frontier in healthcare. By combining adaptability with personalization, this approach enables tailored medical interventions that maximize patient outcomes.

Keywords: Adaptive clinical trials, Precision medicine, Personalized treatment, Targeted therapies

Significance | Combining adaptive clinical trials with precision medicine transforms healthcare by enabling real-time, personalized interventions tailored to individual patient needs.

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Editor Elham Farsi, Ph.D., And accepted by the Editorial Board February 12, 2023 (received for review January 01, 2023)

Introduction

Precision medicine is a method of achieving optimal patient outcomes by combining clinical and molecular patient data to better understand the disease's biological foundation (Desmond-Hellmann, 2012). This technique directs the selection of the best targeted therapy based on specific patient characteristics and unique molecular features of a cancer. In comparison to conventional population-based cancer treatment, this approach aims to maximize patient outcomes while offering better safety profiles. Clinical trials are the scientific evaluation of investigational drugs, technologies, or biologics in human volunteers for safety and efficacy. Examples include chemotherapy agents, blood products, and gene therapies. Candidate therapeutic drugs usually undergo a protracted, strictly controlled multi-phase clinical trial procedure prior to being approved by the US Food and Drug Administration (FDA). In order to advance toward a more individualized strategy, considerable changes to the existing designs of clinical trials will be required. An inventive, quick-turnaround approach to assessing targeted treatments is the adaptive trial design. Researchers can change the course of a participant's study plan or the trial itself with this design, which enables them to assess study data that has accumulated at potential interim time periods (Berry et al,2012).

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Please Cite This:
Khan, M. S. S., Rashid, M. H. O., et al. (2023). Adaptive clinical trials in precision medicine: A framework for enhancing cancer research and patient care. Journal of Precision Biosciences, 5(1), 1-9, 5802

Table 1 shows common trial adaptation types. This paper aims to provide an overview of adaptive design, showcase ongoing research projects that employ this innovative methodology, and explore the ways in which precision medicine is being advanced by genomic and biomarker research.

A single trial structure can address several problems through the use of adaptive design trials (Mucke et al,2017). Cancer research is changing its approach to relying on trials to determine a treatment's safety and efficacy as well as the best way to administer it and to identify the patients who will benefit the most from it. Adaptive trials employ a technique whereby the treatment arms made available to patients who are later enrolled can be changed based on the findings of an interim analysis.

An adaptive design is characterized as one that permits after-the-trial alterations to the trial and/or its statistical protocols without compromising the trial's integrity and validity (Chow et al,2015). The goal is to improve the speed, flexibility, and efficiency of clinical studies. These trial designs are often known as "flexible designs" because of the degree of flexibility required. The trial's flexibility does not imply that it can be changed at any time. Modifications and modifications must be prepared ahead of time and based on data gathered during the study. As a result, an adaptive design clinical trial is defined as "a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from study subjects" in the FDA's recently released draft guidance for the industry on adaptive design clinical trials. At predetermined points during the study, analyses of the gathering data are carried out, either with or without formal statistical hypothesis testing (Food and Drug Administration, 2010).An adaptation is a modification made to the trial protocol and/or statistical procedure during the course of a clinical study. The eligibility requirements, study dosage, treatment duration, study outcomes, laboratory testing protocols, diagnostic protocols, criteria for evaluation, and assessment of clinical responses are examples of trial methods. Randomization, study design, study hypotheses, sample size, data monitoring and interim analysis, statistical analysis plan, and/or data analysis techniques are examples of statistical procedures (Chow et al,2015).

2. Adaptive Clinical Trials: Flexibility Redefined

Adaptive clinical trials are a unique approach to clinical research that breaks away from the rigidity of standard approaches and introduces a dynamic, responsive framework. This revolutionary change has great potential for quickening the pace of drug discovery, increasing the effectiveness of clinical trials, and eventually providing patients with faster, more efficient treatments.In conventional clinical trials, investigators follow a predetermined procedure that is set before the investigation starts. This fixed design incorporates predetermined elements such as sample size, treatment arms, and endpoints. Modifications to these characteristics are often forbidden once the study has begun, restricting the trial's responsiveness to emerging data (Chow and Chang, 2017). Instead, real-time adjustments and flexibility are welcomed in adaptive clinical trials, which enable investigators to modify the study design in response to interim analyses (Korn & Freidlin, 2010).

2.1 The I-SPY 2 Trial: Pioneering Adaptive Design in Breast Cancer Research

Adaptive trials' flexibility is most visible in their ability to change critical aspects during the course of the investigation. This involves modifying the treatment arms, randomization ratios, and patient population variables. The implementation of advanced statistical techniques facilitates this flexibility and guarantees the preservation of the trial's findings in the face of continuous adjustments (Wang et al., 2017).One important instance of the adaptive method in operation is the breast cancer I-SPY 2 experiment. This novel trial design dynamically adjusts in response to clinical and genomic data. I-SPY 2 enables quick identification of potential treatments and eliminates ineffective ones by adapting dynamically to new information (I-SPY 2 TRIAL, 2010).

In I-SPY 1, chemotherapy was given before surgery, and biomarkers were compared to tumor response using magnetic resonance imaging (MRI), pathologic residual disease at the time of surgical excision, and 3-year disease-free survival. Pathologic complete response (pCR) varied by molecular subset, according to the study; hormone receptor-positive/HER2-negative carcinomas were linked to the lowest pCR (9%) and hormone receptor-negative/HER2-positive carcinomas had the highest pCR (45%). Pathologic complete response is defined as the absence of an invasive tumor in either the breast or axillary lymph nodes (Esserman et al,2012). I-SPY 1 further demonstrated that pCR predicted recurrence-free survival within a molecular subgroup.(Esserman et al,2012). According to the study, the most accurate indicator of illness persistence following chemotherapy was MRI volume (Hylton et al,2012). The framework for integrating biomarkers and imaging with common techniques and real-time research data access was built by this work, and it will be utilized in I-SPY 2.

The adaptive design trial I-SPY 2 (investigation of serial studies to predict your therapeutic response with imaging and molecular analysis 2) (ClinicalTrials.gov numbers: NCT01042379) compares the efficacy of standard therapy alone with novel drugs in combination with standard chemotherapy. Bayesian statistics are used in this trial. Figure 1 depicts the trial schema. Compatibility with taxane therapy and HER2-directed therapy, comparability with taxane plus trastuzumab, rationale for efficacy in breast cancer, targeting important pathways/molecules in breast cancer, such as HER2, insulin-like growth factor receptor (IGFR),

phosphatidylinositol 3-kinase (PI3K), macrophages, Akt, Akt and mitogen-activated protein kinase (MAPK), PI3K and mitogen-activated protein/extracellular signal-related kinase (MEK), death receptor, cMET, and mammalian target of rapamycin (mTOR); and fitting the strategic model for single/multiple molecular targeting in breast cancers.

The research will feature two control arms: standard neoadjuvant chemotherapy (weekly paclitaxel or paclitaxel with trastuzumab for HER2+ patients), followed by doxorubicin and cyclophosphamide. A minimum of 20 patients and a maximum of 120 patients will be used to test each investigational medication (Barker et al,2019). To be eligible, a patient must have a blood sample drawn, an MRI, and a core biopsy in addition to presenting with a lesion of at least 3 cm. Patients must meet one of the following criteria: they must be HER2-positive and MammaPrint low-risk and ER-negative, MammaPrint high-risk, or MammaPrint low-risk and ER-positive.6. The trial is examining the following agents: ABT-888, a PARP inhibitor, AMG 386 (angiopoietin 1 and 2 neutralizing peptibody), AMG 479 (monoclonal antibody against IGFR1) plus metformin, MK-2206 (Akt inhibitor) with or without trastuzumab, AMG 386 and trastuzumab, T-DM1 (trastuzumab conjugated to cytotoxic agent mertansine) and pertuzumab (monoclonal antibody targeted against HER2), as well as pertuzumab plus trastuzumab (Kim et al,2018).

A blood sample and an extra MRI are collected prior to surgery. The patient's pCR is evaluated during surgery, and their overall and disease-free survival are monitored. The link between pCR and signatures of interest is modeled, with the randomization probability adjusted to allow for accumulating data, based on the biomarkers evaluated at baseline (Douillard et al,2012). During the trial, agents who do well within a particular molecular signature subgroup of interest will advance more swiftly and receive a matching biomarker to be investigated in a small-scale phase III trial. Agents will be eliminated for futility if they show no improvement in any molecular signature when compared to usual treatment. It is possible to add more agents to the experiment as existing agents are discarded or graduate. One of the medications, ABT-888, was just licensed and is showing encouraging outcomes in patients with triple-negative breast cancer. When ABT-888 was combined with normal chemotherapy, patients with triple-negative breast cancer had a 52% positive response rate (pCR), while those who had standard chemotherapy alone had a 26% pCR. (Mok et al,2019). The National Cancer Institute, the FDA, over 20 academic institutions, numerous pharmaceutical companies, labs, non-profit organizations, and advocates are working together on this public-private partnership trial, which is overseen by the Foundation for the National Institutes of Health Biomarkers Consortium. The advocates have contributed to the development of patient materials, reviewed consent paperwork and protocol design, and staffed a hotline and email inbox where patients undergoing the experiment and prospective patients could speak with a counselor specially trained in the trial (Godin-Heymann,2017).

3. Adaptive Trials and Precision Medicine

In this section, I highlight adaptive design as a novel clinical trial innovation that arose from new research approaches and a deeper comprehension of the intervention under evaluation. Adaptive design trials are associated with the growth of precision medicine in this set of circumstances.

A personalized or precision medicine approach involves customizing treatment to meet the needs of each patient. Predictive, preventative, personalized, and participatory medicine, or "P4" medicine, is how it is frequently portrayed. Advances in molecular medicine have given rise to a new scientific field called pharmacogenomics, which aims to comprehend the molecular mechanisms of drug response, while observations of highly variable drug responses have prompted the creation of a new scientific discipline from genetics, biochemistry, and pharmacology: pharmacogenetics. In this innovative technique, medicine selection and dosing are guided by patients' gene variants. In order to assess precision medicine treatments, match patients in well-responding subgroups with potential treatments, enhance access, and assess efficacy sooner and more effectively, a number of adaptive measures have been implemented.The BATTLE-2 study, or The Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination 2, is an illustration of an adaptive trial for a precision medicine intervention (Garralda et al. 2019) (Figure 2). Based on mutation profiles, results from the "adaptive phase" are used to randomize patients to different medications or combinations (Kim et al,2011).

An example of an adaptive design is an accrual design. Afterwards the initial "learning phase," patients are randomly assigned to the experimental arm or the control arm, and this ratio changes during the "adaptive phase" to increase the proportion of patients in the arm performing better and to increase the statistical power to detect clinical benefit (Garralda et al. 2019). The term "adaptive enrichment" describes changing the patient eligibility requirements. For example, if analysis reveals that a particular subgroup responds better than others, the trial can be "enriched" by changing its enrollment criteria to either exclusively or mostly include members of this subgroup (Thorlund et al. 2018). Phase II to phase III trials can be conducted in a seamless adaptive trial design (Adam et al, 2010).

Precision medicine research teams have produced a large portion of the literature on adaptive trials, including instructions for their reporting and implementation. They are drawing attention to issues surrounding their use, but they are also offering solutions (Garralda et al., 2019; Pallmann et al., 2018). Since every experiment is unique,

obtaining informed consent and effectively informing patients of the risks and benefits may present challenges (Garralda et al., 2019). Funders may choose not to approve adaptive trials because they are dubious about their validity or because they are inexperienced in assessing them (Garralda et al., 2019; Pallmann et al., 2018). Adaptive design may not be well-known to regulators (Pallmann et al., 2018).

Overall, a variety of factors—many of which are local, contingent, and practical—can raise doubts about the effectiveness of adaptive trials. Adaptive trial proponents contend that these issues can be resolved through open preparation, cautious implementation, and critical analysis of the findings. Additional abilities in planning, performing, and assessing adaptive design trials, as well as statistical, mathematical, and modeling knowledge, would be required. Their wider use is both encouraged and discouraged, sometimes by the same authors (like Pallmann et al., 2018, from the clinical medicine side) and regulatory documents (FDA, 2019), since many clinicians are not trained in their usage and regulators are unsure about their potential to avoid problems that the standard randomization and bias-reducing measures are in place for. On the cautious side, it is stressed that, although trials may be shorter, randomization and blinding are still the most trustworthy measures of impartiality in clinical research. Relying too much on non-randomized, non-blinded experiments and avoiding control groups is one particularly harmful technique. On the positive side, innovative designs like seamless design trials and multi-arm trials are considered well-understood, morally sound, and effective methods of conducting clinical research.

4. Ethical and Regulatory Issues

Clinical trials for precision medicine include many of the same ethical and legal concerns as clinical trials in general. This covers appropriate clinical practice, confidentiality, privacy and data sharing, and disclosure policies. The FDA released a draft advice in 2010 titled "Adaptive Design Clinical Trials for Drugs and Biologics" in response to the growing usage of adaptive design trials. The guidance covered topics such as adaptive design trial characteristics, when and how to communicate with the FDA during preparation, and considerations for analysis (Gold et al,2013). The requirement that all modifications be described prior to trial beginning is the main regulatory concern when organizing adaptive design trials (Berry et al,2012). Restricting data access during an adaptive-design trial is crucial since the trial's design may change as more data becomes available (Berry et al,2011). To protect the trial's integrity, the likelihood of a patient being assigned to one arm or the other must be kept confidential. For instance, patients with biomarker "X" would be more likely to be assigned to the research arm containing medicine "Y" if they were exhibiting a better response to drug "Y." Patients might receive medicine "Y" outside of the trial if the blinded research scientists discovered the secrecy of this superior response during the trial.

A companion diagnostic device used in vitro (IVD) settings to identify a responder group is a new biomarker that is evaluated in clinical trials alongside medication efficacy. FDA approval for an IVD companion diagnostic device is required separately. An experimental device exemption is used for the IVD companion diagnostic device research. The "Guidance for Industry and Food and Drug Administration Staff – In Vitro Companion Diagnostic Devices" draft guidance was released by the FDA in 2011 (Gold et al,2013).

Adaptive design trials are complicated, involving logistical and procedural implementation-related operational challenges. Some institutional review boards may be unfamiliar with the design, and doubts remain concerning how best to provide proper informed consent (Gaydos et al,2013). The increased start-up expenses needed to invest in integrating the process and information technology infrastructure are a significant factor to take into account (Nelson et al,2010). However, once set up, this can be used for further research. Response-adaptive randomization in adaptive design clinical trials, like the ones previously discussed, results in lower enrollment and, consequently, fewer opportunities for harm as a higher proportion of patients are randomly assigned to study arms where similar patients have previously responded (Lipsky et al,2013).

5. Nursing Implications

Recent advances in basic research have altered our understanding of cancer, as well as our approach to patient care and expectations for patient outcomes. Nurses are being asked to incorporate biomarker-based care into all facets of nursing practice, including clinical trials, as precision oncology therapy becomes a reality. In order to provide safe, competent, and efficient care to patients taking part in contemporary clinical trials, one must possess the necessary knowledge, abilities, and experience in imaging, appropriate treatment options (including standard cancer care as well as potential clinical trials), and additional or required disease biomarkers. In this situation, nursing practice necessitates understanding of proper patient follow-up, interdisciplinary service and counseling referrals, and clinical trial administration duties (Gaydos et al,2019).

Nursing organizations like the American Nurses Association, the Oncology Nursing Society (ONS), and the International Society of Nurses in Genetics (ISONG) have developed competencies, curricula guidelines, and in some cases outcome indicators to incorporate the genetic, genomic, and clinical trials perspective into nursing education, practice, and research. This is done to ensure that nurses are adequately prepared to perform in the new era of clinical trials and the human genome. **Table 2** integrates

Table 1. The Most-Common Types of Adaptive Settings in Modern Clinical Trials

Stopping early (or late, that is, extending accrual) with a conclusion of either superiority or futility
Adaptively assigning doses to more-efficiently assess the dose-outcome relationship
Dropping arms or doses
Seamless phases of drug development within a single trial
Changing the proportion of patients randomized to each arm
Adaptively homing in on an indication or responder population
Adding arms or doses
Changing accrual rate

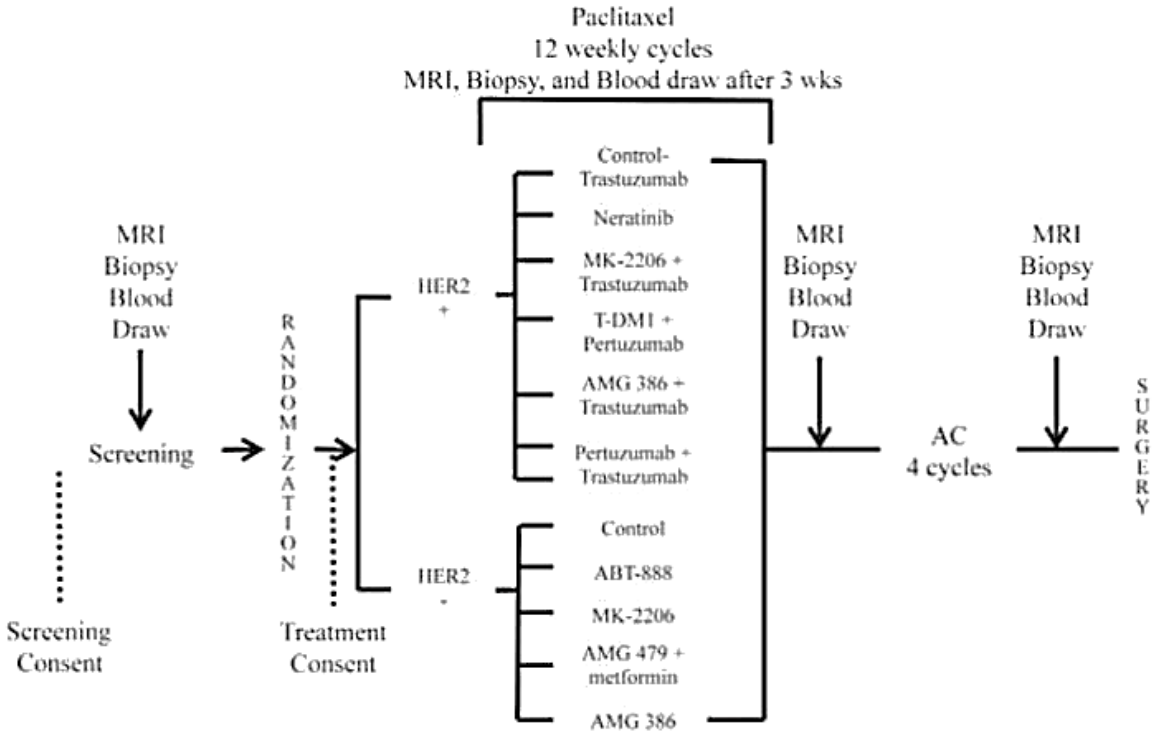

Figure 1. I-SPY 2 Schema trial design for I-SPY 2 (investigation of serial studies to predict your therapeutic response with imaging and molecular analysis 2). HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; AC, anthracycline (doxo-rubicin) and cyclophosphamide (Cytoxan)

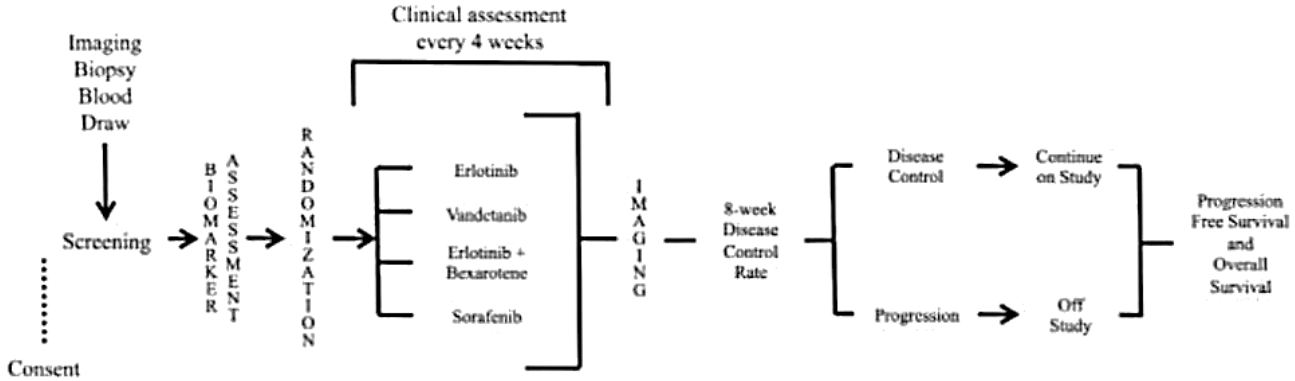

Figure 2. Battle schema trial design for Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE)

Table 2. Oncology Nursing Competencies for Clinical Trials in the Era of Precision Medicine

Functional Area	Competencies
Protocol compliance	Facilitates compliance with research protocol and good clinical practice Demonstrates an understanding of the relationship of genetics/genomics to a clinical trial
Trial-related communication	Utilizes multiple communication methods to facilitate implementation of clinical trials. Facilitates referrals for specialized genetic/genomic services for clients as needed and as allowed per protocol
Informed consent process	Demonstrates leadership in ensuring patient comprehension and safety during initial and ongoing clinical trial informed consent discussions. Advocates for the rights of clients for autonomous, informed genetic/genomic related decision-making and voluntary action.
Documentation	Ensures collection of source data and completion of documentation that validates the integrity of the study Collects personal, health, and developmental histories that consider genetic, environmental, and genomic influences and risks, per protocol
Ethical issues	Demonstrates leadership in ensuring adherence to ethical practices during the trial in order to protect the rights, well-being, and privacy of participants and the collection of quality data Identifies ethical/ancestral, religious, legal, fiscal, and societal issues related to genetic/genomic information and technologies Defines issues that undermine the rights of all clients for autonomous, informed genetic and genomic-related decision-making and voluntary action

components of the ONS Oncology Clinical Trials Nurse Competencies (Oncology Nursing Society.2013) with the American Nurses Association's genetic and genomic nurse skills (Quinlan et al,2010). Both sets of competencies were created in direct response to professional nurses' requests for a complete curriculum on their specific content area and standardization of role expectations. These competencies include aspects of protocol compliance such as good clinical practice and understanding the relationship between genetics/genomics and a clinical trial; the informed consent process, which assists patients in understanding all aspects of the trial; subject recruitment; trial-related communication; research subject management; ethical issues; and professional development.

As imaging plays a larger role in determining treatment effectiveness, as in I-SPY 2, where MRI volume correlates with risk of residual disease, and the importance of image guided biopsy in both the I-SPY and BATTLE trials, oncology nurses will need to understand imaging as it relates to the clinical trial they are conducting or the type of imaging required for their patient care responsibilities. This involves properly preparing the patient, supporting the patient during the operation, safely caring for the patient after imaging, assisting with imaging preparation when necessary, ensuring a safe atmosphere, and conducting specialized interventions during imaging as needed. A recent paper from the Royal College of Nursing emphasized these qualities (Royal et al,2013). Although biomarkers may be more directly relevant to adaptive design trials, nursing societies have not yet developed competencies in this area. These competencies may be developed as the field advances. The oncology nurse is an integral part of the interdisciplinary team needed for efficient clinical trials in the era of precision medicine (Longini,et al, 2018).

6. Challenges and Future Directions in Integrating Adaptive Trials and Precision Medicine

The integration of adaptive clinical trials with precision medicine is a promising avenue for advancing healthcare, but it faces several challenges that necessitate strategic solutions and ongoing research efforts. The complexity brought about by the statistical techniques used in adaptive design is one of the main obstacles. Sophisticated statistical tools are necessary to manage real-time adjustments in adaptive trials without sacrificing the validity and reliability of the results due to their dynamic nature. To address these complexities and guarantee the robustness of adaptive trial outcomes, researchers are actively working to develop sophisticated statistical approaches, such as Bayesian methods (Jaki et al., 2019).

Furthermore, regulatory considerations create significant barriers to the seamless integration of adaptive trials and precision medicine. The special features and real-time adjustments that come with adaptive designs may be difficult to incorporate into the current regulatory frameworks, which are frequently made for conventional trial structures. Researcher collaboration, regulatory bodies, and industry stakeholders are working together to harmonize regulatory guidelines. Fostering innovation while maintaining patient safety requires the establishment of a regulatory framework that strikes a balance between regulatory rigor and flexibility (Woodcock & LaVange, 2017).

Data management issues and privacy concerns are two additional challenges resulting from the integration of adaptive trials and precision medicine. In terms of infrastructure and analytics, the generated data is diverse and complex, encompassing real-time adaptations and genomic information. Simultaneously, reliance on sensitive molecular data raises privacy concerns, necessitating robust mechanisms to ensure patient data security and confidentiality. To address these data challenges, ongoing research initiatives focus on standardizing data formats, implementing advanced encryption techniques, and developing anonymization methods.

One significant financial obstacle to precision medicine is the high expense of genomic testing. The cost implications of personalized approaches, which heavily rely on genomic information, may prevent patients from accessing these cutting-edge therapies. Cost-effective genomic testing models are being actively investigated by researchers. These models include collaborative efforts to negotiate bulk purchasing agreements, automation, and advances in sequencing technologies. With the goal of reducing financial obstacles to implementation, precision medicine should become more widely available and economically feasible (Lu & Lee, 2019).

Despite these obstacles, continuous research projects are improving the integration of precision medicine and adaptive trials and opening the door for possible remedies. At the forefront of these efforts are cost-effective genomic testing models, standardized data formats, privacy safeguards, regulatory harmonization, and advanced statistical methodologies. Furthermore, a patient-centric strategy is becoming more popular, incorporating patients in the decision-making process to address ethical issues and improve the general acceptance and success of these cutting-edge approaches (Calvert et al., 2018).

To summarize, while there are challenges in integrating adaptive clinical trials and precision medicine, ongoing research directions show promise for overcoming these obstacles. The changing environment highlights the necessity of cooperative efforts among scientific, regulatory, and industry domains in order to improve statistical techniques, handle privacy and data management issues, investigate affordable models for genomic testing, and include patient-centric decision-making processes. As these solutions develop, they not only help precision medicine and adaptive trials work together more successfully, but they also usher in a new era of individualized, effective, and efficient healthcare.

7. Conclusion

In conclusion, the fusion of precision medicine and adaptive clinical trials is a revolutionary force in healthcare, heralding a paradigm shift toward individualized and effective treatment modalities. The dynamic nature of adaptive trials, combined with the personalized strategies of precision medicine, has the potential to revolutionize the development of targeted therapies. The path toward this integration is difficult but full of promise, from the complex statistical techniques guaranteeing the validity of adaptive trial results to the difficulties in handling various data sources and resolving privacy issues. Looking ahead, the future of healthcare promises exciting opportunities, fueled by ongoing advancements. As statistical methodologies evolve to accommodate the complexities of real-time adjustments, and regulatory frameworks adapt to align with the distinct characteristics of adaptive testing and precision medicine, a more collaborative and streamlined landscape emerges. The emphasis on patient-centered approaches not only addresses ethical concerns, but it also improves the acceptance and success of these novel methodologies.

In conclusion, the combination of precision medicine and adaptive trials offers hope for the future of healthcare by enabling the ongoing improvement of individualised treatments based on real-time data. As these solutions advance, they not only help to successfully integrate adaptive trials with precision medicine, but also usher in a new era of personalized, efficient, and effective healthcare. The ongoing advancements in statistical methodologies, regulatory frameworks, and patient-centered approaches provide a glimpse into a future in which healthcare is not only targeted but also responsive and inclusive, ultimately improving patient outcomes and redefining the landscape of modern medicine.

Author contributions

S.S.K., M.H.O.R., M.K.A.B., and M.M.H. made significant contributions to the manuscript. M.S.S.K. conceptualized and designed the study. M.H.O.R. was involved in data collection and drafting the manuscript. M.K.A.B. conducted data analysis and interpretation. M.M.H. critically reviewed and revised the manuscript for intellectual content. All authors reviewed and approved the final version of the manuscript.

Acknowledgment

The authors were grateful to their department.

Competing financial interests

The authors have no conflict of interest.

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