Texila International Journal of Academic Research
ISSN: 2520-3088
DOI: 10.21522/TIJAR.2014.11.02.Art015

Adaptive Study Design Methodology vs. Standard Randomized Clinical Trial in Different Therapeutic Area: A Review

Srividhya Narasimhan[1*], Vishnubalaji Radhakrishnan[2]
[1]*Clinical Research Department, Texila American University, Mauritius*
[2]*Translational Cancer and Immunity Center, Qatar Biomedical Research Institute (QBRI) 2, Doha, QATAR*

Abstract

The aim of this review is to explore the learning outcome and understanding how the adaptive study design helps in current scenario of drug development in various therapeutic areas compared to traditional randomized clinical trials with respect to Dose Finding, identification of Maximum tolerated dose (MTD), fewer subjects, short duration, increases success rate of study objective, yields better knowledge of treatment effect like better estimates of sub-group effects or dose-response relationship. One of the major advantage of this study design is that potential changes are approved prior hand by regulatory authorities and ethics committee, hence there is no need to submit the protocol amendment and also logistics for the change in treatment is also planned upfront and researchers are given full flexibility to respond towards unexpected events and there are several options proposed upfront to introduce any new doses, amend endpoints. The conclusion is that the use of Adaptive designs appears to be increasing in certain diseases and in some of the diseases it is still underutilised. FDA and other regulators, researchers are still exploring how and the extent to which they may be incorporated into the evaluation of experimental therapies bearing in mind that focus will be mainly in feasibility, validity, flexibility, integrity and efficiency. As the new regulatory guideline are already established, future investigations of adaptive designs could examine ongoing dynamics in trials and based on this project, there are some suggestions to be given to the researchers to include the adaptive design or methodology to be indicated in the study title which certainly helps to retrieve the data easily.

Keywords*: Adaptive Design, Adaptive Dose- Finding, Randomized Clinical Trial, Standard Clinical Trials.*

Introduction

Drug Development Cost has substantially increased in the past few decades however this has neither not translated to increase in the number of approved drugs nor in the greater success rates in clinical trials. Clinical trials have typically been conducted in three steps. [1]: The trial is planned; it is carried out in accordance with the plan; Once the data is prepared, it is evaluated in accordance with a predetermined analysis plan. This procedure is simple, but it is obviously rigid because it does not allow for adjustments that could be wanted or required over the course of the trial. An option is provided by adaptive designs (ADs). Assumption-busting strategies have been referred to as "planning to be flexible" [2], "driving with one's eyes open" [3], or "taking out insurance" [4]. According to the BioMed Tracker, upon review of the results from 4,275 clinical trials during the period of 2003 to 2010, the overall success rate for trial drug approval or intervention was only 9% (3).There are many factors influencing in the low success rate, among which increasing complexity of bringing potential experimental therapiesto trial is one of the important factor. A novel approach

Received: 23.03.2024 ***Accepted: 24.04.2024*** ***Published on: 30.04.2024***
****Corresponding Author: srividhya_2011@hotmail.com***

to overcome this challenge is accomplished by modifying trial design features during the trial which is termed Adaptive study design. The decision will be made by the researchers based on the data collected throughout the trial.

The defining characteristic of all ADs is that results from interim data analyses are used to modify the ongoing trial, without undermining its integrity or validity [5]. Preserving integrity and validity is crucial. In an AD, data are repeatedly examined. Thus, we need to make sure they are collected, analysed and stored correctly and in accordance with good clinical practice at every stage. Integrity means ensuring that trial data and processes have not been compromised, e.g. minimising information leakage at the interim analyses [6]. Validity implies there is an assurance that the trial answers the original research questions appropriately, e.g. by using methods that provide accurate estimates of treatment effects [7].

Adaptive study design unlike traditional designs, is proposed to be more flexible and accumulate data to alter the ongoing research trials without undermining the integrity and validity of the trial whereas the traditional designs does not permit modifications during the course of enrolment and follow-up phase, and where the efficacy and safety are understood only after the trial is completed [8]. This results in enhancing clinical research by cutting on the time and the cost factor which is most warranted in conducting clinical trials for a pharmaceutical development. Also to be noted that both the traditional and adaptive trial designs have important differences, like the differences in the planning and conduct of these studies, so too are the reasons and interpretation of bias[9]. Major Regulatory agencies such as US FDA began encouraging the use of adaptive design methods and also European Medicines Agency (EMA) have identified the validity of adaptive trial designs and provided guidance on how researchers and Pharmaceuticals should consider their regulatory considerations during the presubmission (i.e., planning/learning phase) and confirmatory phases[10]. This study design is defined as ‘planning to be flexible’ ‘driving with one’s eyes open’ or ‘taking out insurance’against assumptions.

A recent review of trials registered on ClinicalTrials.gov showed a large increase in thenumber of adaptive design trials completed since 2006: there were only 10 registered adaptivetrials before 2006, but 133 registered from 2006 to 2013 however as per the basic data search through publications, there are no data published yet on the adaptive study designs in recent years. Hence, this literature review is prepared by organizing adaptive trials data after 2013 for which data posted in Clinical Trials.gov is utilised. The list of the Randomizedclinical trials conducted from year 2013-2018 in which analysis of the number of adaptive trialsincluding drug and device in all the phases of clinical trials in different indications were studied.

Methodology

A comprehensive Feasibility study was conducted to choose the appropriate literature search engine to extract the data on the list of adaptive study design conducted between year 2013 – 2019. The list of sources included in the literature search are PubMed, Cochrane search, Clinical Study Data request website and Clinical Trials.gov.

Table 1. Types of Adaptive Designs and its Definitions. Source: PubMed (nih.gov)

Type of adaptive design	**Definition**
Adaptive dose-finding	These clinical trials usually occur in early-phase research for dose identification in future studies. These studies allocate patients to multiple different treatment doses and patient responses are assessed at interim analyses. Trial design is thenadapted to allocate more patients to the treatment doses of interest, reducing allocation of patients to doses that appear non-informative.
Adaptive randomization	A study design in which accumulating results are observed and the randomization scheme is adjusted so that patients enrolled later in the trial have a higher probability of being randomised to the treatment arm that was more effective among earlier patients in the trial.
Seamless Phase II/III	A study design that combines the objectives of the Phase II investigational stage with the Phase III efficacy or confirmatory stage into a single study protocol moving from one stage to the second stage without stopping the patient enrolment process.
Biomarker adaptive	This method allows adaptations to trial design based on interim analysis of the treatment responses of biomarkers, such as genomicmarkers. This design can be used to select patient populations for subsequent trials, identify the natural course of a disease, achieve early detection of a disease and/or help in developing personalized medicine.
Sample size re-estimation	A study design using a flexible sample size adjustment or re-estimation based on interim analysis of accumulating data.
Multiple adaptive	This refers to a trial that incorporates multiple adaptive designs into a single study.

Adaptive treatment-switching	A study design allowing the investigator to switch a patient's treatment from an initial assignment to an alternative treatment dueto apparent lack of efficacy, disease progression or safety issues associated with the initial treatment.

Table 1 describes the phrases derived from the common forms of adaptive study designs: Adaptive dose-finding, adaptive randomization, adaptive treatment switching, Biomarker adaptive, adaptive seamless, sample size re-estimation and Multiple Adaptive.

The results informed the choice of databases for the main review was restricted to ClinicalTrials.gov database where it was found that search criteria were user friendly, better flexibility, improved filtering records, data completeness and searching options[11]. Even unpublished data was able to retrieve based on the therapeutic area with the crux of the information. The search was restricted to dates between 01/01/2013 and 31/12/2018.

Strategy Used for Data Sources and Search

Adaptive design related search in terms of Indications and different phases was an iterative process with the chosen terms from the feasibility study on the sources such as Clinical study Data request.com, Cochrane, PubMed search engines and scoping exercise using Clinical Trials.gov. The search terms were applied to trials meeting the inclusion criteria using the Boolean OR operator. There are certain limitations due to time constraints to perform the quality check by the second reviewer.

Eligibility Criteria

The below are the eligibility list taken for the review:

1. Interventional Clinical Trials including Device Trials
2. Early Phase, Phase II, III & Phase IV
3. Therapeutic Indication
4. Time Period Between 01/01/2013 to 31/12/2018
5. Trial documents posted in English in Clinical Trials.gov

Data Synthesis and Analysis

The following information was collected from the included trials and recorded on an Excelspreadsheet:

1. List of Interventional Clinical Trials conducted during 2013- 2018 as per the ClinicalTrial Registry
2. Number of Adaptive trials among those clinical trials during 2013-2018 as per the Clinical Trial Registry.
3. Number of standard trials in leading Therapeutic area during 2013-2018
4. Number of Adaptive trials in leading Therapeutic area during 2013-2018
5. List of Interventional standard Early Phase, Phase II, Phase III and Phase IV studiesduring 2013-2018
6. List of Adaptive Early Phase, Phase II, Phase III and Phase IV studies during 2013-2018

Main Outcome Measures

1. Number of Adaptive Clinical trials Vs Standard Clinical Trials in Leading TherapeuticArea
2. Number of Adaptive Clinical Trials in Early Phase and Phase II – I

Results and Discussion

Interventional Clinical Trials including drug and device clinical trials from Phase I – IV conducted only in Humans during the period of 2013-2018 were selected for literature review which aimed to understand the number of adaptive study methodology being used in

clinical trial phases and reported in various diseases. Among the systematic review, it was found that 1557 studies with adaptive designs were used during the above indicated period and for this project, sample size of 18 disease condition were selected based on the disease prevalence criteria and its impact in the pharmaceutical development. Based on the analysis, it is identified that 1012 adaptive clinical trial designs were used during the clinical trial implementation.

Table 2. Results on the Comparison of Standard Randomized Clinical Trials VsAdaptive Study Designs. Substantial Variability has been Observed in the Posted Trial Designs and Especially in the Terminology Described in the Title of the Clinical Trial. Source: Clinical Trials.gov

Indication	**Number of Standard Randomized**	**Adaptive study designs**
Endocrine System Diseases	9012	64
Eye Diseases	3930	28
Arthritis	3276	21
Carcinoma	7991	61
Depression (Includes Depressive Disorders and	2855	80
Digestive System Diseases (Includes Gastrointestinal	13298	77
Epilepsy (Includes Epileptics)	593	19
Heart Disease *(Includes Cardiac, Coronary, and*	8373	69
Hypertension	3120	27
Immune system diseases	11240	126
Kidney Diseases	3760	29
Liver Diseases	4088	35
Lung Diseases *(Includes Pulmonary Diseases)*	8204	61
Lymphoma	2504	16
Respiratory Tract diseases	11664	86
Skin Diseases	7549	35
Urologic disease	5265	39
Vascular Diseases Including Disorders	12356	86
Virus Diseases	4740	53

From the review, Table 2 elaborates that researchers/Pharmaceutical sponsor used adaptive designs prominently in Immune system diseases with the number of trials conducted 126, following which the Respiratory and vascular diseases with the number of registered trials of 86 which is also schematically represented in Figure 2.

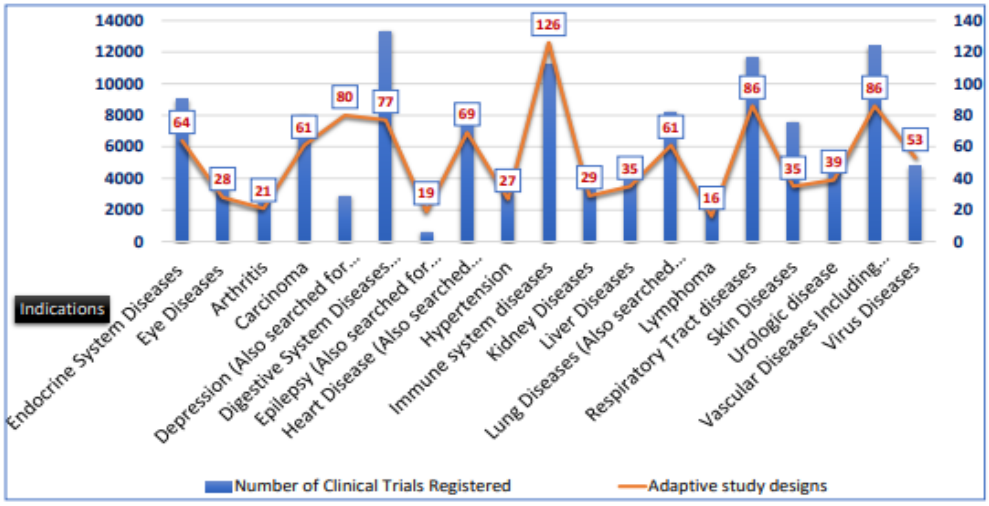

Figure 1. Number of Adaptive Study Designs from the Standard Randomized Clinical Trials in the Selected Disease Condition. Source: PubMed (nih.gov)

Table 3 summarizes the list of adaptive study designs extracted from the selected disease condition listed in the below table and upon analysis,the types of adaptive designs used in each trial were listed. The trials were selected to understand the different types of adaptive study design employed , its significance and the brief description are tabulated.

Table 3. Types of Adaptive Study Design, Description & its Significance. Source: Clinical Trials.gov

CLINICAL TRIALS.GOV IDENTIFIER	THERAPEUTIC AREA	TITLE	DESCRIPTION	TYPES OF ADAPTIVE DESIGNS
NCT00674635	Immune System Diseases	Phase II Study Evaluating the Safety and Efficacy of GSK315234A in Patients With Rheumatoid Arthritis	This is a randomized, double-blinded, placebocontrolled adaptive, dose finding study to investigate the safety, tolerability, PK, PD and efficacy of single and repeat intravenous infusions of GSK315243A in patients with active rheumatoid arthritis. The study	ADAPTIVE DOSE FINDING STUDY

			is divided into 2 parts: Part A is an adaptive, dose finding phase which will provide safety, tolerability, PK and PD on single intravenous infusions. Part B is a repeat dose phase which will provide safety, tolerability, PK, PD and efficacy following repeat intravenous infusions of a selected dose level.	
NCT01555710	Small Cell Lung Cancer	Study of Palifosfamide-tris in Combination With Carboplatin and Etoposide in Chemotherapy Naïve Patients With ExtensiveStage Small Cell Lung Cancer (The MATISSE Study	This is a multinational, multicenter, randomized controlled, open-label, adaptive study to evaluate the efficacy of PaCE chemotherapy in chemotherapy naive subjects with extensive-stage SCLC. Eligible subjects will be stratified according to age, gender, and Eastern Cooperative Oncology Group (ECOG) performance status, and randomized in a 1:1 ratio to receive either PaCE or CE chemotherapy. The study design uses	ADAPTIVE GROUP SEQUENTIAL APPROACH

			an adaptive group sequential approach with sample size re-estimation at the interim analysis	
NCT00502775	Immune System Diseases	An Adaptive Phase II Study to Evaluate the Efficacy, Pharmacodynamics, Safety and Tolerability of GSK2586184	This is an adaptive, dose ranging, Phase II study to investigate the relationship between repeat doses of GSK2586184 and the pharmacodynamic effect and clinical efficacy in patients with active systemic lupus erythematosus (SLE). This study will also investigate the safety and tolerability of repeat doses of GSK2586184	ADAPTIVE DOSE RANGING
NCT03447990	Heart Diseases	Study Evaluating the Safety, Tolerability and Preliminary Pharmacokinetics and Pharmacodynamics of MYK-491	This is a a two part study. The first part is a randomized, crossover, double-blind, placebo-controlled, two cohort, sequential ascending single dose study. All patients will receive placebo and active doses of MYK491.The second part is a randomized, parallel,	ADAPTIVE RANDOMIZATION

			doubleblind, placebo-controlled, sequential ascending multiple dose study. All patients will receive placebo and/or active doses of MYK-491.	
NCT02898662	Lung Diseases	A Phase 2 PlaceboControlled, Randomized, Double Blind, Adaptive Dose Trial of the Safety and Efficacy of Inhaled AZD1419 in Adults With Eosinophilic, Moderate to Severe Asthma	The study has a withdrawal design.The patients will receive 13 once weekly inhaled doses of the study drug (AZD1419 or placebo). Treatment is initiated with 6 doses of the study drug on top of their ICS/LABA controller medication. Prior to the 7th dose of the study drug the LABA is withdrawn. The following 3 doses are given when ICS is tapered down. Dose 7 is given on top of 100% of their ICS, dose 8 is given on top of 50% of the ICS dose, which is then tapered down to 25% the following week and withdrawn completely prior to dose 10 of the study drug. During	ADAPTIVE DOSE DESIGN

			the last 3 weeks of treatment (ie last 4 doses), the study drug is given as monotherapy. SABA is used as reliever medication during the whole study period. Primary endpoint is Loss of asthma control, defined as any of the following criteria: a) An increase of ACQ-5 to 1.5 or more b) A reduction of 30% or more in morning peak expiratory flow (PEF) from baseline on 2 consecutive days c) At least six additional reliever inhalations of SABA in a 24-hour period relative to baseline on 2 consecutive days and d) An exacerbation requiring systemic corticosteroids. When the endpoint is met, patients will resume their regular ICS/LABA controller medication and will be followed for an additional 4 weeks, when they do an Early Discontinuation (ED) Visit and will	

			thereafter leave the study. For patients not loosing their asthma control, the full Observational period is up to week 52, when they will do an End of Treatment Visit (EOT). Study procedures are the same on ED and EOT Visits.	
NCT00976560	DEPRESSION	A Six Week Randomized, Double-blind, Multi-center, Placebo-controlled, Exploratory, Adaptive Design Study to Explore the Antidepressant Properties of the p38 MAP Kinase Inhibitor GW856553 Compared to Placebo in Adult Subjects With Major Depressive Disorder	In this randomized, double-blind, multi-centre, placebo controlled, exploratory, adaptive design study, the antidepressant and plasma cytokine lowering effects of the GW856553 will be investigated in adult subjects diagnosed with MDD. Subjects will receive oral doses of GW856553 or placebo for six weeks. Safety tolerability, pharmacokinetics and pharmacodynamics, defined as biomarkers in blood and clinical symptoms, will be assessed. The primary endpoint is the change from baseline associated	ADAPTIVE SAMPLE SIZE REESTIMATION

			with GW856553 versus placebo at Week 6 in the Bech (6-item HAMD-17) score. Interim analyses of the primary endpoint will be performed throughout the study to potentially adapt the study design by changing the randomization ratio and/ or reducing the total number of subjects to be randomized into the study. Exploratory analyses will be performed by associating changes in cytokine levels and selected clinical symptoms; PK/PD modelling will also be used to identify the most sensitive clinical and biological markers.	

It is evident from the review of Clinical Trials.gov that adaptive methodology design predominantly used in phase II trial after the interim analysis as presented in Table 4. After the phase I trial, a phase II trial which is conducted to evaluate the investigational drugs' therapeutic effects at the recommended dose. The outcome in terms of the efficacy in Phase II trials are often short term[12]. When a new drug or device showspromising efficacy, a Phase III trial will be conducted with a longer term as a confirmatory assessment. Sequential design in contrast to the one stage study design uses the accumulated data to perform an interim analysis from which the results are taken into consideration to adaptively change the study plan. Detailed comparison on the number of clinical trials for each phases represented graphically in Figure 2.

Table 4. Adaptive Study Designs in Different Clinical Trial Phases. Source: Clinical Trials.gov

Clinical Trial Phases	Total Number of clinical trials	Adaptive trials
Early Phase 1	19759	198
Phase 2	23412	291
Phase 3	12591	91
Phase 4	10498	42

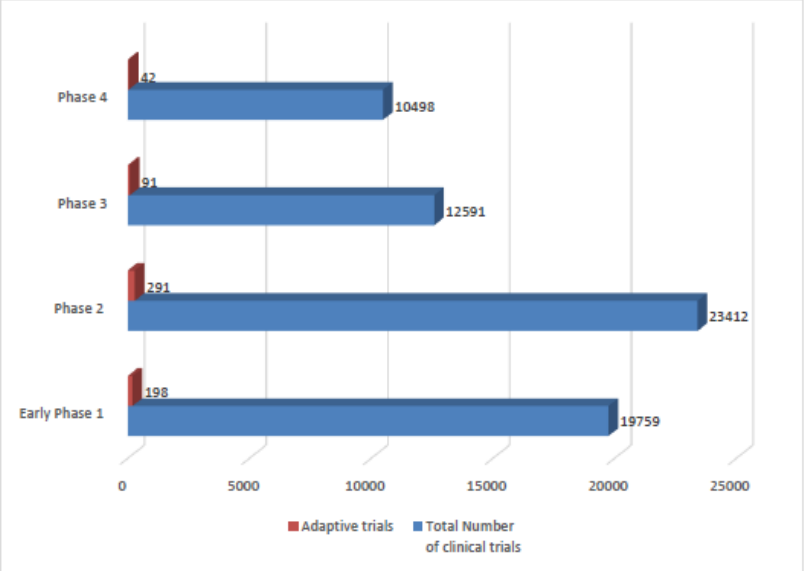

Figure 2. Number of Adaptive Trials in Different Phase of the Clinical Trials Conducted During 03-2018. Source: Clinical Trials.gov

Limitations

The limitations for this project as the main data source Clinical Trials. gov posed some issues in terms of the methodology used in the adaptive trials which could not be retrieved, and methods were redundant in register. Adding to this, since all the registered clinical trials up to were included for analysis to understand the current trends, studies without the final results, unpublished studies were also taken for review and also the device studies not classified under Phase studies[13]. Given the limitations, results are not void as the objectives of this project is to investigate the types of Adaptive Design trials being undertaken in differentphases of clinical trials in the sampled therapeutic area within a specified duration.

Conclusions

A general overview of the current trends of Adaptive design implementation in the clinical trials were discussed and list of studies from each adaptive type were listed with the brief description. Due to the limitations in the inability to extract the study results for all trials fromClinical Trials.gov using the search terms, extensive review of each adaptive trial designs couldnot be analysed. The conclusion is that the use of Adaptive designs appears to be increasing incertain diseases and in some of the diseases it is still underutilized. FDA and other regulators,researchers are still exploring how and the extent to which they may be incorporated into the evaluation of experimental therapies bearing in mind that focus will be mainly in feasibility, validity, flexibility, integrity and efficiency. As the new regulatory guideline are already established, future investigations of adaptive designs could examine ongoing dynamics in trialsand based on this project, there are some suggestions to be given to the researchers to include the adaptive design or methodology to be indicated in the study title which certainly helps to retrieve the data easily.

References

[1] Friedman FL, Furberg CD, DeMets DL.2010, Fundamentals of clinical trials, New York: Springer; 4th ed.

[2] Shih WJ. 2006, Plan to be flexible: a commentary on adaptive designs. Biometrical J.; 48:656–9.

[3] Berry Consultants 2016. What is adaptive design?. http://www.berryconsultants.com/adaptive-designs. Accessed 7 Jul 2017.

[4] Campbell G. 2013, Similarities and differences of Bayesian designs and adaptive designs for medical devices: a regulatory view. Stat Biopharm Res.; 5:356–68.

[5] Chow SC, Chang M, Pong A. 2005, Statistical consideration of adaptive methods in clinical development. J Biopharm Stat.; 15:575–91.

[6] Fleming TR, Sharples K, McCall J, Moore A, Rodgers A, Stewart R. 2008, Maintaining confidentiality of interim data to enhance trial integrity and credibility. Clin Trials.; 5:157–67.

[7] Bauer P, Koenig F, Brannath W, Posch M. 2010, Selection and bias—two hostile brothers. Stat Med.; 29:1–13.

[8] Posch M, Maurer W, Bretz F. 2011, Type I error rate control in adaptive designs for confirmatory clinical trials with treatment selection at interim. Pharm Stat.; 10:96–104.

[9] Graf AC, Bauer P. 2011, Maximum inflation of the type 1 error rate when sample size and allocation rate are adapted in a pre-planned interim look. Stat Med.; 30:1637–47.

[10] Graf AC, Bauer P, Glimm E, Koenig F. 2014, Maximum type 1 error rate inflation in multiarmed clinical trials with adaptive interim sample size modifications. Biometrical J.; 56:614–30.

[11] Deepak L, Cyrus Mehta.2016 Adaptive Designs for Clinical Trials. J Med 375:65-74.

[12] Kristian T , Jonas H , Jay J, Edward J Mills. 2018, Key design considerations for adaptive

clinical trials: a primer for clinicians. BMJ 2018;360:k698.

[13] Rajiv Mahajan, Kapil Gupta. 2010, Adaptive design clinical trials: Methodology, challenges and prospect. Indian J Pharmacol.; 42(4): 201–207.