Master's Thesis of Medical Science

Adaptive Clinical Trial Design: Current Status and Key Considerations by Disease and Trial Phase

적응적 임상시험의 최신 현황과 질환 및 임상시험 단계에 따른 주요 고려사항

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Abstract

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Introduction: An adaptive design is a clinical trial design that allows for modification of a structured plan in a clinical trial based on data accumulated during pre-planned interim analyses. This flexible approach to clinical trial design improves the success rate of clinical trials while reducing time, cost, and sample size compared to conventional methods. The purpose of this study is to identify the current status of adaptive design and present key considerations for planning an appropriate adaptive design based on specific circumstances. This will be achieved by providing an outline of adaptive design for various indications and clinical trial phases.

Methods: I searched for clinical trials conducted between January 2006 to July 2021 in the Clinical Trials Registry (clinicaltrials.gov) using keywords specified in the Food and Drug Administration (FDA) Adaptive Design Clinical Trial Guidelines. In order to analyze the adaptive designs used in selected cases, I classified the results according to the phase of the clinical trial, type of indication, and the specific adaptation method employed.

Results: A total of 267 clinical trials were identified on clinicaltrials.gov. Among them, 236 clinical trials actually applied adaptive designs and were classified according to phase, indication types, and adaptation methods. Adaptive designs were most frequently used in Phase 2 clinical trials and oncology research. The most commonly used adaptation method was the adaptive treatment selection design. In the case of COVID-19, the most frequently used designs were adaptive platform design and seamless design.

Conclusion: This study highlights the latest trends in adaptive clinical trials in various situations. Through this study, I expect to

provide valuable insights and considerations for the implementation of adaptive clinical trials in different diseases and stages.

Keyword: adaptive clinical trial, interim analysis, flexibility, reducing sample size, cost-effectiveness, protocol modification

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Chapter 1. Introduction

1.1. Study Background

In the clinical pharmaceutical field, extensive efforts have been made in clinical trials to minimize the number of participants, costs, and time while ensuring safety and efficiency.[1] In line with this trend, adaptive design in clinical trials has recently gained attention. Adaptive design allows the modification of ongoing studies based on the accumulated data of a pre-planned interim analysis in clinical trials. Further, adaptive design increases the flexibility and scope of clinical trials.[2] Through these features, adaptive design could offer advantages in reducing the risk and accelerating decision-making for drug development (

Figure 1).[2, 3]

Recently, regulatory administrations, including the U.S. Food and Drug Administration (FDA), have recommended using adaptive designs and have also described the principles and considerations for the appropriate use of adaptive designs.[4] However, adaptive design clinical trials are not routinely applied compared to conventional clinical trials. Several studies have discussed the challenges regarding adaptive design, such as lack of education and

insufficient information, which could discourage the implementation of adaptive design clinical trials.[5]

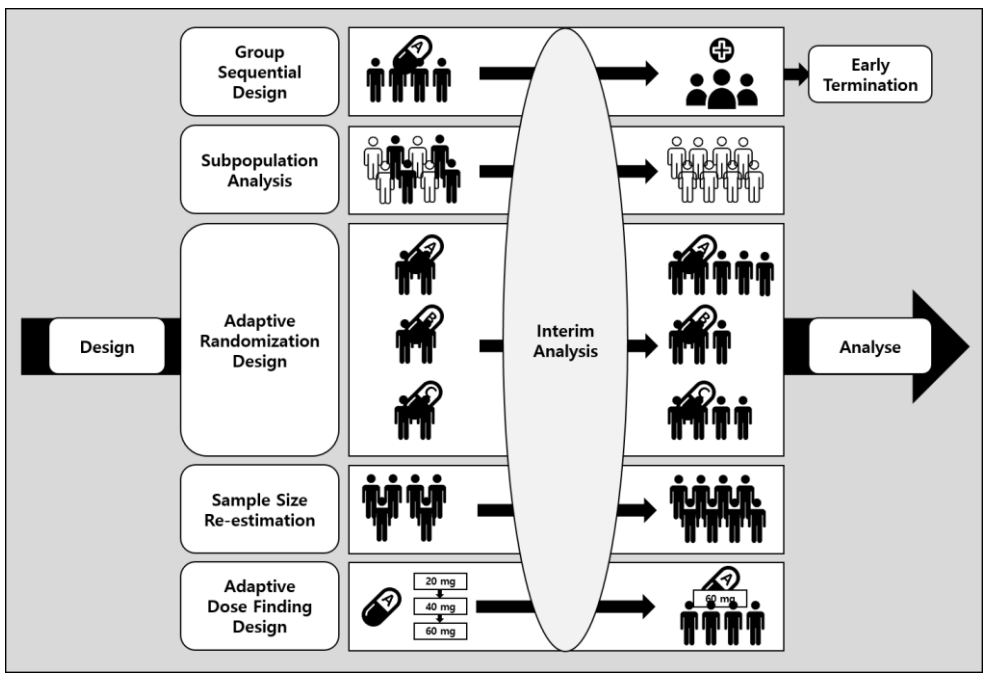

Figure 1. Schematic of an example of adaptive design using pre-planned interim analysis and adaptation

Schematics of common examples of adaptive design. With adaptive design, modifications using pre-planned interim analysis during a clinical trial are allowed. Group sequential design, adaptive designs for subpopulation analysis, adaptive randomization design, adaptive sample size re-estimation, and adaptive dose-finding design from top to bottom are shown.

1.2. Types of adaptive design

Adaptive designs can be applied in various types depending on the protocols. In this study, cases were categorized according to the the adaptive designs in the following nine types based on the FDA's "Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry" document and several previous studies.[5-9]: Group sequential design, adaptive randomization design, adaptive subpopulation analysis, adaptive sample size re-estimation, adaptive dose finding design, adaptive hypothesis design, multiple adaptive design, seamless phase design.

1.2.1. Group sequential design

Group sequential is a clinical trial design that evaluates results according to the predefined criteria of efficacy or futility, allowing the trial to be terminated before all participants are enrolled.[4] In group sequential design, compared to the conventional clinical trial with a fixed number of subjects, if the investigational product meet the efficacy criteria, the trial can be terminated for early success. In contrast, if the investigational product showed futility in the interim analysis, the trial could be terminated due to early failure.

On both occasions, it has the advantage of reducing research resources, time, cost, and risk of patients being exposed to ineffective products.

In the case of a group sequential design, it is important to set a threshold value that determines the efficacy and utility criteria of a clinical trial. Simultaneously, the risk of type I error and statistical power should be considered when statistically setting the threshold value.[10] In this regard, two boundary methods are well-known. First is the Pocock boundary, which sets the same boundary value each time during an interim analysis. Second is the O'brien–Fleming boundary, which sets a large boundary value at the beginning of the interim analysis when the amount of data is small and sets smaller boundary values for subsequent interim analysis when the amount of data is sufficient.[4]

Once boundary values are established, an interim analysis according to an appropriate prospective analysis plan can lead to early termination based on futility or efficacy criteria.[4] In this case, it is important to establish clear termination criteria. As the group sequential design aims to terminate the clinical trial early, much fewer safety data would be confirmed than in the original protocol. Therefore, in some cases, early termination criteria require ethical reasons or highly persuasive results.

1.2.2. Adaptive randomization design

Adaptive randomization is a clinical trial design wherein the randomization rate of additional enrolled subjects can be modified based on efficacy or safety data from an interim analysis.[11] Adaptive randomization designs are broadly classified into two categories: covariate- and response-adaptive randomization.[4, 12, 13]

Covariate adaptive randomization is a method of randomly assigning subjects to treatment groups by considering the baseline characteristics of newly enrolled subjects, based on the cumulative results of the baseline characteristics of the previously enrolled subjects and randomization ratio.

The second method is response-adaptive randomization, which determines a new randomization ratio based on the results of previously enrolled subjects using interim analysis. An example involves the "play the winner" approach, wherein a less efficacious treatment group is eliminated via interim analysis, and subjects are subsequently randomized to a treatment group that is considered more effective.

Similar to other adaptive designs, adaptive randomization methods offer the advantages of minimizing time, sample size, and

data variability, and they could provide ethical benefits by assigning a higher proportion of newly registered subjects to the treatment group with better efficacy.

There are some considerations regarding the use of adaptive randomization methods. Adaptive randomization design may have limitations in the context of large-scale trials or clinical trials with long treatment durations because of the dependence of subject randomization on the response observed in the previous subjects.[6] Moreover, changing the randomization ratio for treatment groups according to the efficacy data carries the risk of increasing the possibility of type I error. Therefore, it is important to validate that the study design is appropriate to use adaptive randomization and to confirm whether the statistical analysis method is suitable for a clinical trial design to assess the possibility of type I error.[4]

1.2.3. Adaptive subpopulation analysis

The adaptive subpopulation analysis method is an adaptive design in which the trial continues only in a specific population or subgroup identified as more responsive to the drug's efficacy through interim analysis. This method has the advantage of obtaining higher power with a smaller number of subjects compared

with conventional clinical trials. Adaptive enrichment design is a representative example of adaptive subpopulation analysis. In the adaptive enrichment design, the trial is conducted in two stages. In the first stage, the subjects are recruited from the entire population. Following an interim analysis at the end of the first stage, it is determined whether the trial should involve the entire population or be restricted to a subgroup characterized by a positive response to a predefined biomarker using the accumulated data.[14, 15]

When planning to switch the target population to a subpopulation, two different types of risks must be considered. First, in a subpopulation analysis, there is a possibility of overlooking potential treatment options, owing to the dilution of the treatment effect within the full population. This can lead to ethical concerns regarding the administration of nonbeneficial treatments to patients. Second, during interim analysis, there is a risk of erroneously selecting a spurious subpopulation, thereby increasing the risk of a type 1 error rate.[16] Therefore, it is important to elucidate the reason behind the more pronounced effect of the drug in a specific patient population based on accumulated data from previous studies or scientific evidence. In addition, if there are criteria for defining a subpopulation, it is crucial to validate these criteria.

1.2.4. Adaptive sample size re-estimation

An adaptive sample size reestimation method allows modifying the number of subjects based on the results of the interim analysis. In clinical trials, sample size is sensitive to the treatment effect. Therefore, inaccurate estimates of treatment effects may increase or reduce the power of the trial, leading to undesired results, such as retaining a drug considered effective or missing a clinically significant finding.[4, 17] By using an adaptive sample size reestimation design, such problems can be prevented.

There are two different methods of adaptive sample size reestimation, that is, using blinded or unblinded data.[4, 18] The blinded sample size reestimation design conducts interim analysis without unblinding the treatment assignment to provide an estimate of a nuisance parameter to update the sample size for the trial.[19] Further, the risk of type I error can be neglected in this method; however, it should be used with caution in the early stages of clinical trials, considering the variability of the variance.[4] In contrast, unblinded sample size reestimation designs use the unblinded interim analysis result to reestimate the size and variability of the treatment effect. This method carries the risk of increasing the

probability of a type I error; therefore, statistical adjustments for the final test analysis are required.[4]

1.2.5. Adaptive dose finding

An adaptive dose-finding design allows for the modification of the treatment group based on the results of an interim analysis. This design is often used in early phase exploratory clinical studies to confirm the appropriate doses of investigational products, such as the maximum tolerated dose (MTD) or minimum effective dose, before the next phase of a clinical trial. The results of the adaptive dose-finding design can be used to establish the doses used in subsequent confirmatory clinical trials. An example of adaptive dose-finding design is the continuous reassessment method. This method adaptively increases the dose evaluated in the early phase trials based on the toxicity observed in the interim analysis to reliably and efficiently estimate the MTD of a new drug.[20]

If a dose group with considerable benefits and risks is identified, additional modifications such as group sequential design, adaptive sample size reestimation, or adaptive randomization for the carry-over treatment arm can be conducted. When several other adaptive designs are applied, a plan for controlling type I errors for each

adaptive design and a specific adaptation rule for selecting treatment arms should be considered.[4]

1.2.6. Adaptive hypotheses design

An adaptive hypothesis design allows for the adaptive modification of primary hypotheses based on interim analysis results. This method could be used when the treatment effect is uncertain in the results with primary endpoint or the relationship between the endpoint and response is unclear.[4] With this case, based on the results of the interim analysis, the single hypothesis of the clinical trial can be replaced with multiple hypotheses, or the null and alternative hypotheses.[5] In addition, if the secondary endpoint represents a better treatment–response relationship than the primary endpoint, the secondary endpoint can be selected after the interim analysis.[6]

When using an adaptive hypothesis design, it is crucial to establish clear standards for modifying the primary endpoint and explain the reason for the modification, as the primary endpoint is directly aligned with the study objective.

1.2.7. Multiple adaptive design

Multiple adaptive designs can be used in a single clinical trial. For example, in an adaptive dose-finding design, a combination of a group sequential and adaptive randomization designs can be applied. The group sequential design allows for the termination of treatment groups that show futility, whereas the adaptive randomization design enables the modification of the randomization ratio based on interim analysis to enroll more subjects in the highly effective treatment group. Because multiple adaptive designs are combined in this method, it is difficult to estimate the probability of a type I error.[4] Therefore, a type 1 error control method for each adaptive design that is applied to clinical trials should be considered.

1.2.8. Seamless phase design

Seamless phase design combines two different phases, that is, the learning and confirmatory phases, into a single clinical trial.[6, 21] There are two types of seamless design: seamless phase I/II and seamless phase II/III.

Generally, the primary objective of phase I clinical trials is to identify the MTD of the investigational products, and that of phase

II clinical trials is to evaluate the efficacy of the MTD. In a seamless phase I/II design for early phase trials, the MTD is determined in phase I, and then patients are assigned to either the MTD or several dose groups around the MTD in phase II subsequently.[22] In this two-stage design, the first stage usually uses a 3+3 design (accelerated titration) or continual reassessment method to get close to a good dose level, and the second stage uses a modified randomization design employing the efficacy and toxicity data.[23]

In a seamless phase II/III design, the exploratory and confirmatory phases are integrated and proceed to phase III by adding more patients to a specific treatment group or by extending the follow-up period while remaining in phase II clinical trials. The most efficacious dose group was observed in phase II, and the effect of the dose group followed immediately to phase III. In this design, the inclusion/exclusion criteria of the enrollment or randomization scheme remain unchanged.[21] Response adaptive randomization or multi-stage drop loser designs are often employed during transition from Phase II to Phase III.[6]

1.3. Considerations for designing an adaptive design

As mentioned previously, adaptive designs offer numerous advantages, including cost and time reductions, in clinical trials. Therefore, the application of an adaptive design is highly recommended for the pharmaceutical industry. However, there are limitations and disadvantages, owing to a modification in the direction favorable to the clinical trial objectives, that must be considered when designing an adaptive design,

Several adaptive designs make it possible to stop clinical trials early to ensure futility or satisfaction with efficacy. The early stopping rule is advantageous because fewer participants are required, which lowers the risk of allocating subjects to ineffective treatment arms. However, in adaptive design studies, treatment effects can be overestimated owing to reliance on relatively small samples of data, which are typically based on the largest observed treatment effects during interim analysis.[4]

This increases the risk of selecting the wrong adaptation methods and potentially missing the detection of a true treatment effect.[4] Therefore, it is important to consider the risk of missing important information. This includes evaluating whether to discontinue treatment for subjects assigned to the early stopped treatment arm or to switch to a more effective treatment arm.[24]

Continued follow-up must be considered when treating the patients with the latter case.

Another consideration for the adaptive design is that it may be susceptible to an increased type I error, which refers to an incorrect rejection of the null hypothesis. This is because of multiple interim analyses and adaptations, which can increase the likelihood of false-positive results. Each interim analysis and adaptation presents opportunities for early termination based on the futility test, sample size reestimation, or endpoint selection based on unblinded analysis, which may increase the type I error rate for the entire study.[4] Therefore, appropriate statistical methods, including control of the overall type I error rate through adaptive design modifications, are crucial to mitigate this risk.

To control type 1 error in adaptive designs, various statistical methods and procedures can be employed. A common method is to estimate the type I error rate for a predefined adaptation rule using simulation methods.[25] A previous study revealed that the cumulative type I error rate increases for each interim analysis conducted. For example, using the traditional fixed-sample threshold of 1.95, the actual type I error rates for a fixed-sample two sided 0.05 significance level are nearly 0.15 after five interim analyses, and

0.20 after 10 interim analyses, which is unacceptably high for clinical trials.[26, 27]

An alpha error-spending function governs the cumulative type I error. The alpha error-spending function refers to the allocation of the overall significance level (alpha) across interim analyses and adaptations, so that sequential testing can be performed while maintaining the overall error probability of the procedure. It relies on the fraction of patients or events observed in a specific interim analysis compared to the total expected or planned number. In each interim analysis, the type I error allocation is determined using the alpha spending function, which corresponds to an adjusted critical value for the test statistic computed in that analysis. The purpose of this function is to control the overall type-I error rate by appropriately distributing the alpha across the interim analyses, allowing adaptive monitoring while maintaining the desired statistical rigor. Using an alpha error-spending function, group sequential designs enable efficient monitoring of accumulated data, allowing for potential early stopping or adaptation of the trial without inflating the overall type-I error rate.[27]

1.4. Study objectives

Although the overall current status and characteristics have been investigated, the specific applications of the adaptive design according to the indication types have not been identified.[5, 28, 29] In addition, the studies analyzing the adaptive design clinical trials did not include phases I and I/II, owing to the low impact on regulatory approvals despite their role in drug development.[28, 29]

The objectives of this study were to update the current statistics on adaptive design methods used in the clinical pharmaceutical industry and to analyze the properties of adaptive design clinical trials from various perspectives, including indication types and phases. The study also aims to suggest key considerations and insights for using adaptive design in various situations, such as the outbreak of a future pandemic.

Chapter 2. Methods

2.1. Data source and search strategy

I summarized ongoing or terminated clinical trials with adaptive design from the clinical trial registry "clinicaltrials.gov" from January 2006 to July 2021. I searched for clinical trials using several keywords① from the FDA's "Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry" document, which provides guidance on the appropriate use of adaptive design. The document describes important principles for designing, conducting, and reporting the results from adaptive clinical trials. The retrieved results were confirmed to determine whether adaptive design was actually used, as included in our pre-determined adaptive design categories.

① We used kewords from FDA's Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry; "adaptive design", "flexible design","adaptive trial", "adaptive method", "adaptive dose adjusting", "adaptive allocation", "sample size adjustment", "biomarker adaptive", "biomarker adjusted", "adaptive hypothesis", "adaptive dose-finding", pick-the-winner", drop-the-loser", "sample size re-estimation", "adaptive randomization", "group sequential", "adaptive seamless "

2.2. Data analysis

The retrieved results were classified based on the phases (Phase I/II/III), indication types (infectious disease, neurology, oncology, metabolic/endocrinology, autoimmune/inflammation, cardiovascular disease, respiratory, healthy subjects, etc.), and adaptive methods to determine which design was most commonly used by phase and indication types. Additionally, I checked the first year posted in the registry and confirmed the trend of adaptive design usage by year.

I have reviewed the study summaries from the clinicaltrials.gov registry to determine the adaptive design utilized in the clinical trial case. If there are any attached research documents, such as a research plan, statistical analysis plan, or case study report, the specific research design should be identified and classified. If the type of adaptive design used in the cases was not clarified or provided in registry, I classified these as 'Unknown'. Regarding the use of multiple adaptive designs in cases, I have confirmed which adaptive designs were used in single cases to determine specific statistics and identify which designs were most frequently used together in multiple adaptive designs.

I specifically identified the adaptive methods used in COVID-19 cases to confirm the application of adaptive design in a pandemic situation. Based on this data, I intend to present key considerations for the application of adaptive design in potential future pandemic situations.

Chapter 3. Results

3.1. Search Results

3.1.1. Overall results

Using pre-determined keywords from FDA guidance, a total of 267 clinical trials conducted until July 2021 were identified on ClinicalTrials.gov. As a result, I analyzed 236 cases in which adaptive design was actually implemented. The total number of adaptive designs used was 292, including all cases of multiple adaptive designs, out of a total of 236 cases. The most commonly used adaptive design in all cases was the adaptive treatment selection design, which was used in 110 (37.7%) out of 236 cases. This was followed by the seamless phase design, which was used in 56 (19.2%) cases, and the group sequential design, which was used in 49 (16.8%) cases (Table 1).

Table 1. Most used adaptive design in all cases

Types of adaptation methods	Number of cases (%)
Adaptive treatment selection	110 (37.7)
Seamless phase	56 (19.2)
Group sequential design	49 (16.8)
Adaptive randomization design	31 (10.6)
Adaptive sample size re-estimation	16 (5.5)
Adaptive sub-population analysis	9 (3.1)
Adaptive hypothesis design	2 (0.7)
Unknown	19 (6.5)
Total adaptive design used (total cases)	292 (236)

In the analysis of clinical trial cases utilizing adaptive design over the years based on search results, it was observed that the utilization of adaptive design showed a gradual increase from 2006 to 2021. Notably, there was a significant surge in 2020 (Figure 2).

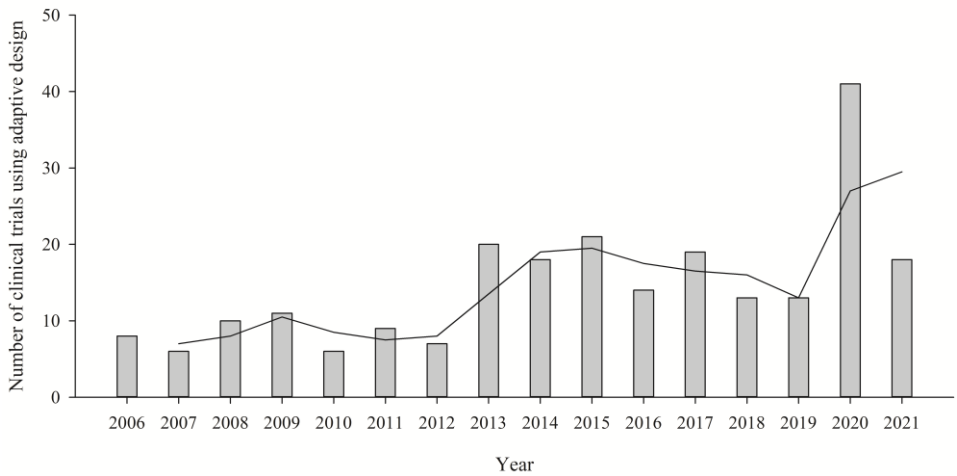

Figure 2. Annual statistics for cases of clinical trial using adaptive design

Number of cases of adaptive clinical trials by year: It has been confirmed that the average number of cases of adaptive clinical trials per year has shown a gradual increasing trend, particularly in 2020 with 41 cases.

3.2. Main Outcome

3.2.1. Adaptive Design Cases by Phases

As a result of classifying a total of 292 adaptive clinical trials by phase, it was found that adaptive design was most frequently used in phase 2 clinical trials. Specifically, there were 97 (33.2%) adaptive designs used in Phase 2, 54 (18.5%) in Phase 2/3, 52 (17.8%) in Phase 1, 49 (16.8%) in Phase 1/2, and 40 (13.7%) in Phase (Figure 3). In the case of phase 1/2 and phase 2/3 clinical trials, most cases were analyzed using a multiple adaptive design because all cases were designed in a seamless phase design (Figure 4).

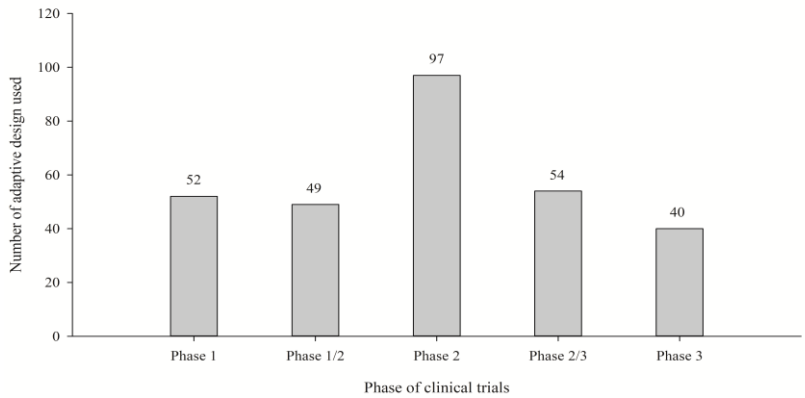

Figure 3. Number of adaptive design used in cases by phase

Number of clinical trial cases using adaptive design: Phase 2 clinical trials had the highest frequency of adaptive design use, with 97 cases identified. This was followed by phase 2/3 trials with 54 cases, and phase 1 trials with 52 cases. Adaptive designs were primarily used in early-phase trials, which typically aim to identify the optimal dosage and validate the efficacy and safety of new drugs.

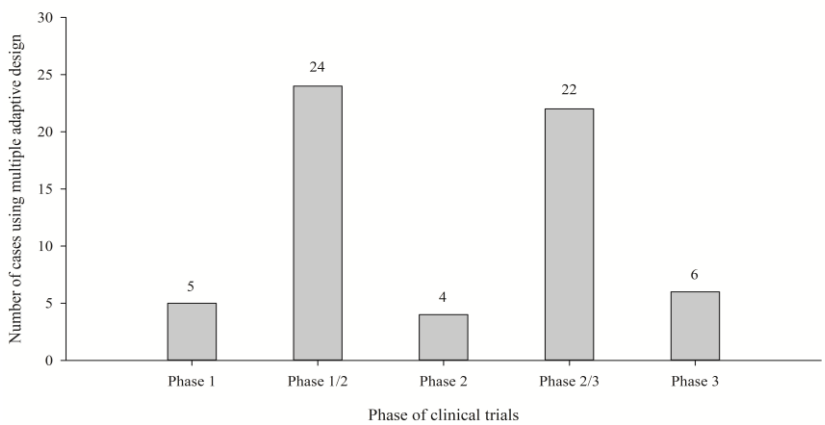

Figure 4. Number of cases using multiple adaptive design by phase

Number of clinical trial cases applying multiple adaptive designs: All cases of Phase 1/2 and Phase 2/3 confirmed the use of seamless phase design, resulting in the incorporation of multiple adaptive features into a single clinical trial. However, only a few instances of multiple adaptive designs were observed in Phase 1, Phase 2, and Phase 3 trials.

The most commonly used adaptive designs were the adaptive treatment selection design in Phase 1 and Phase 2, and the group sequential design in Phase 3 (Table 2). In the case of Phase 1/2 and Phase 2/3, all cases were classified as seamless phase designs, which are the most commonly used designs. When the seamless phase design was excluded, the adaptive treatment selection design was used the most, just like in phase 1 and phase 2.

Table 2. Most used adaptive designs in cases by phase

Phase	Adaptation methods	Number of cases (%)
Phase I	Adaptive treatment selection	33 (63.5)
Phase I/II	Seamless phase design	27 (55.1)
Phase II	Adaptive treatment selection	44 (45.4)
Phase II/III	Seamless phase design	29 (53.7)
Phase III	Group sequential design	21 (52.5)

3.2.2. Adaptive Design Cases by Indication types

As a result of classifying a total of 292 adaptive clinical trials by indication types, it was found that adaptive design was most frequently used in oncology clinical trials. Specifically, there were 82 (28.1%) adaptive designs used in oncology, 52 (17.8%) cases in neurology, 40 (13.7%) cases in autoimmune/inflammatory diseases, 36 (12.3%) cases in infectious diseases, 22 (7.5%) cases in metabolic/endocrinology, 18 (6.2%) cases in cardiovascular disease, 11 (3.8%) cases in respiratory diseases, 9 (3.1%) cases in healthy subjects, and 22 (7.5%) cases for other indications (Figure 5).

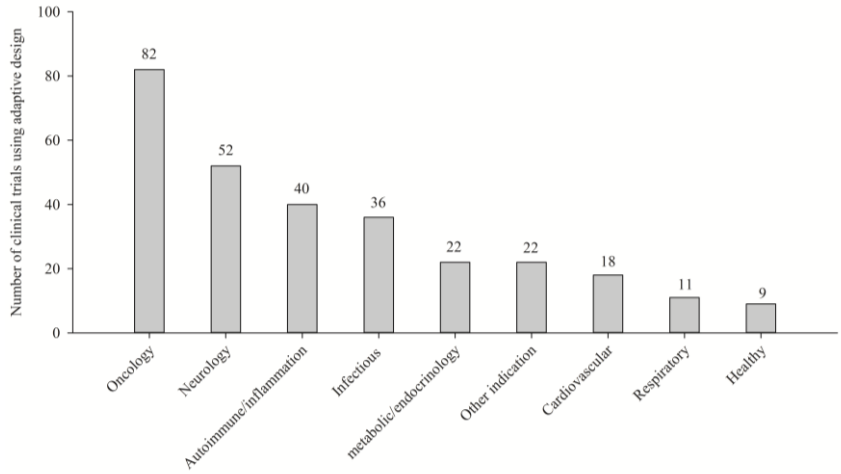

Figure 5. Number of adaptive design used in clinical trial cases by indication types

Number of cases of adaptive design applied to clinical trials by indication type: Oncology clinical trials showed the highest frequency of adaptive design use with 82 cases, followed by neurology with 52 cases, and autoimmune/inflammatory disease with 40 cases. Most of the adaptive designs were used in clinical trials involving patients, while they were least utilized in clinical trials involving healthy subjects.

The most commonly used adaptive design was the adaptive treatment selection design in all indication types, except for infectious disease, where the seamless phase design was used the most (Table 3).

Table 3. Most used adaptive designs in cases by indication types

Indication types	Adaptation methods	Number of cases (%)
Neurology	Adaptive treatment selection	25 (48.1)
Oncology	Adaptive treatment selection	25 (30.5)
Autoimmune/Inflammation	Adaptive treatment selection	15 (37.5)
Infectious disease	Seamless phase design	12 (33.3)
Metabolic/Endocrinology	Adaptive treatment selection	9 (40.9)
Healthy	Adaptive treatment selection	6 (66.7)
Cardiovascular disease	Adaptive treatment selection	5 (27.8)
Respiratory disease	Adaptive treatment selection	5 (45.5)

Unlike the overall results, in the case of oncology clinical trials, the adaptive treatment selection design was predominantly used only in phase 1. In Phase 2 and Phase 3, the group sequential design was used the most with 8 cases each. In the case of Phase 1/2 and Phase 2/3, the seamless phase design was used the most. When excluding seamless phase design, the most commonly used design in both phase 1/2 and phase 2/3 was adaptive treatment selection design, similar to phase 1 cases (Table 4). For statistics

on other indication types by phase are presented in the supplementary table.

Table 4. Number of cases using multiple adaptive design in oncology clinical trial by phase

Oncology	Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Total (%)
Adaptive treatment selection	9	7	4	3	2	25 (30.5)
Group sequential design	1	0	8	2	8	19 (23.2)
Seamless phase	0	8	0	9	0	17 (20.7)
Adaptive randomization design	0	0	8	1	0	9 (11.0)
Adaptive sample size re-estimation	0	0	1	1	2	4 (4.9)
Adaptive sub-population analysis	0	0	3	0	1	4 (4.9)
Unknown	1	0	3	0	0	4 (4.9)
Adaptive hypothesis design	0	0	0	0	0	0 (0.0)

3.2.3. Adaptive Design Cases in COVID-19 clinical trial

To validate the findings of adaptive design in COVID-19 clinical trials, I conducted an additional analysis specifically focusing on COVID-19 cases within the category of infectious disease cases. There were a total of 25 adaptive designs used in COVID-19 clinical trial cases. Specifically, there were 9 (36.0%) cases of adaptive platform design, which was the highest number. This was followed by seamless phase design with 8 (32.0%) cases, and group sequential design with 3 (12.0%) cases (Table 5).

Table 5. Number of cases using multiple adaptive design in COVID-19 clinical trial by phase

COVID-19	Total (%)
Adaptive platform design	**9 (36.0)**
Seamless phase	8 (32.0)
Group sequential design	3 (12.0)
Adaptive treatment selection	2 (8.0)
Adaptive sample size re-estimation	1 (4.0)
Adaptive randomization design	1 (4.0)
Adaptive hypothesis design	1 (4.0)
Adaptive sub-population analysis	0 (0.0)
Unknown	0 (0.0)

Chapter 4. Discussion

An adaptive clinical trial design adds flexibility to conventional clinical trials by allowing changes in the planned protocol based on the results accumulated during the interim analysis. In this study, I evaluated the frequency of each adaptive design used across different diseases and phases, provided an updated overview, and suggested considerations when designing future adaptive clinical trials based on specific indications and clinical trial phases.

A total of 236 cases with 292 adaptive designs were searched and classified by phase and indication type, with nine different categories of predetermined adaptive design. Among the 292 adaptive designs, adaptive treatment selection was used the most, with a total of 110 cases, followed by 56 cases of seamless phase design.

Of the 110 adaptive treatment selection designs, in most cases, 96 used an adaptive dose-finding design in phases I, I/II, and II to determine the optimal dose before the follow-up stage. The adaptive dose-finding design was used the most in Phase 1, accounting for 63.5% of all Phase 1 cases. In other words, the adaptive dose-finding design was mainly applied in the early stages of drug development, such as in optimal dose-finding studies or confirming the maximum tolerated dose and dose-limiting toxicity. In addition, the use of an

adaptive design was also observed in two-stage or seamless-phase designs to determine the optimal dosage range in the next stage. These results indicate that the adaptive design is frequently used to rapidly determine the optimal dose in early phase or two-stage clinical trials.

In phase III clinical trials, the group sequential design was used most frequently, with 21 (52.5%) cases. Because phase I clinical trials require a large number of subjects, high cost, and time compared to phase I and II trials, this study aimed to reduce the number of subjects, cost, and time required for the trial by using futility tests through early termination. These results showed that although early clinical trials focused on allowing modifications to treatment arm selection for efficient optimal dose exploration, later-phase trials aiming at the safety and efficacy of the optimal dose focused on reducing the sample size and time cost for trial by applying futility tests through the group sequential design.

Based on the classification results by indication type, adaptive designs were the most frequently used in clinical trials for oncological diseases (82 cases), followed by 52 cases for neurology, and 40 cases for autoimmune/inflammatory disease. In the oncology and neurology clinical trials, there were 134 adaptive designs in 292 cases. Because of the importance of safety results and high risk of exposure to futile investigational drugs when conducting clinical trials of new drugs in life-threatening diseases such as

cancer, early termination based on efficacy and futility tests is important.[30] Accordingly, among the adaptive designs used in oncology clinical trials, adaptive treatment selection design was the most common with 25 cases, followed by group sequential design, with a total of 19 cases.

The least used adaptive design was the adaptive hypothesis design, with one case each in a clinical trial with an infectious disease and healthy subjects. One of the key considerations in adaptive clinical trials is the risk of type 1 error arising from allowing modifications. Because the primary endpoint of a clinical trial is related to the desirable outcome, it may be difficult to control the type 1 error risk that arises from changing the endpoint through interim analysis compared to other adaptive designs. For these reasons, the adaptive hypothesis design has been used less frequently.

Of the 36 identified infectious disease clinical trials, 16 focused on the development of COVID-19 vaccines. The most important aspect of the emergence of new infectious diseases such as COVID-19 is the rapid start of vaccine clinical trials to track the epidemic curve and enroll enough cases.[31] As a result, adaptive platform design was used the most with nine (36.0%) cases, followed by seamless phase design. The adaptive platform design is a type of master protocol. Not all master protocol designs are assumed to be adaptive; however, the platform design is classified as adaptive because of its adaptive properties of adding or dropping out treatment groups that satisfy a specific

decision algorithm (adaptive treatment selection) and a modification of the randomization scheme between the treatment arms (adaptive randomization design). The COVID-19 Outpatient Pragmatic Platform Study (COPPS), a multistage adaptive platform protocol for rapid vaccine development since the emergence of COVID-19 developed by Stanford University[32], is an example of a platform design, and three cases were confirmed to have used this design in our results. The structural features of the platform design, which allow multiple treatment groups to be included in one clinical trial, can be used for rapid vaccine or treatment development or discovery in the event of a pandemic. In the case of the recent COVID-19 clinical trial, it seems that the focus was on rapidly discovering vaccines and treatments for newly emerging infectious diseases rather than on existing treatments in line with the pandemic situation. There were also eight cases (32.0%) of seamless phase-design for COVID-19 clinical trials, which seemed to focus on the rapid development of vaccines or treatments. Based on the confirmed adaptive designs of COVID-19 cases in this study, I conceived a schematic of adaptive design in a pandemic situation to suggest considerations for future researchers (Fig. 7). As mentioned earlier, during a pandemic, the development of a rapid vaccine or treatment is crucial. This scheme proceeds from multiple candidate treatments and proposes a design that identifies the efficacy and safety of all registered candidates in a clinical trial. When designing a seamless phase, the optimal dose of all valid

candidates can be identified in phase 1, and the efficacy and safety at the corresponding dose can be evaluated in phase II. By conducting an interim analysis during the trial, it was possible to determine whether the treatment groups met the futility or success criteria. This enables the reduction of unnecessary subject numbers and allows for modifications to the adaptive randomization scheme based on the observed efficacy data, leading to a reduction in time and cost requirements. The schematic suggests the use of group sequential design and adaptive randomization design as adaptive design features. However, according to the purpose, an adaptive subpopulation analysis design can be used if biomarkers are identified during subject screening and divided into biomarker−positive and biomarker−negative groups; various other adaptive designs can also be used concurrently. By presenting the corresponding schematic, it is expected that an appropriate application of an adaptive design can be presented in the event of a future pandemic.

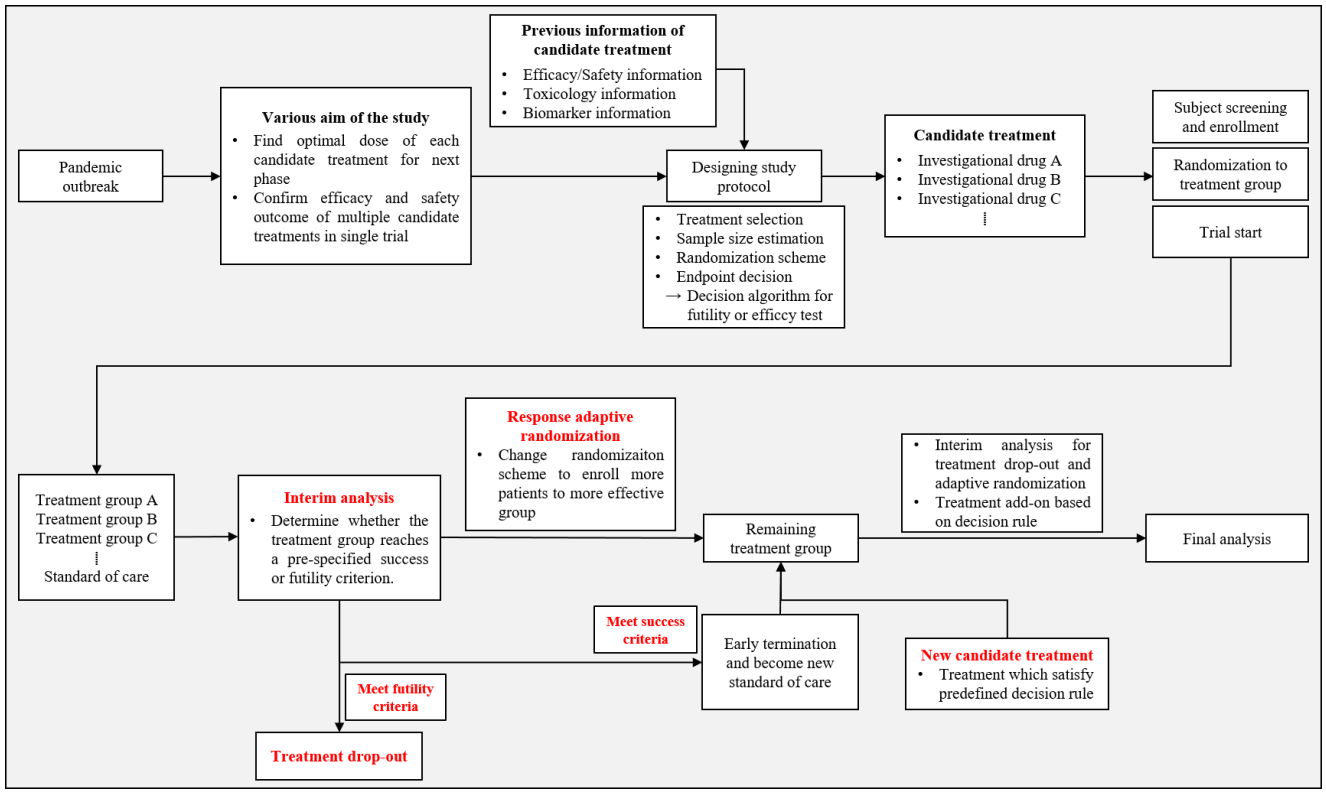

Figure 6. Adaptive design recommendation scheme for future pandemic situation

Schematic of adaptive design that can be used in new infectious diseases such as COVID-19. The part indicated in red in the corresponding schematic is the part to which the adaptive design features are applied.

This study has several limitations. First, the types of adaptive design used to classify the search results were selected based on previous studies and FDA guidelines. However, although I have provided specific explanations for each adaptive design, there might be some confusion in their classification owing to variations in the terminology used in other studies (Table 6).

Table 6. Various categories of adaptive design in previous studies and FDA guidance

FDA- Adaptive designs for clinical trials of drugs and biologics (2019)	Adaptive design clinical trials: a review of the literature and ClinicalTrials.gov (2017)	Adaptive design methods in clinical trials – a review (2008)	Adaptive Design - Recent Advancement in Clinical Trials (2016)	Key design considerations for adaptive clinical trials: a primer for clinicians (2017)	Evolution of global clinical trials with adaptive design (2021)
Group sequential design	Adaptive dose-finding	Adaptive randomization design	Group sequential design	Sample size reassessment	Adaptive group sequential design
Adaptations to the sample size	Adaptive hypothesis	Group sequential design	Error-spending design	Response adaptive randomization	Sample size re-estimation
Adaptations to the patient population	Adaptive group sequential	Sample size re-estimation design	Sample seize re-estimation design	Dropping of inferior treatment arms	Phase I/II or II/III two stage seamless design
Adaptation to treatment arm selection	Adaptive randomization	Drop-the-loser design	Pick-the-winner and add-arm design	Adaptive enrichment	Adaptive enrichment
Adaptations to patient allocation	Seamless phase 2/3	Adaptive dose finding (e.g., dose escalation) design	Adaptive randomization design	Seamless design	Master protocol with adaptive design
Adaptations to endpoint selection	Adaptive treatment-switching	Biomarker-adaptive design	Adaptive dose-escalation design		Multiple adaptive design
Adaptation to multiple design feature	Biomarker adaptive	Adaptive treatment-switching design	Biomarker-adaptive design		Adaptive treatment-switching
	Pick-the-winner/drop-the loser	Hypothesis-adaptive design			Adaptive hypothesis design
	Sample size re-estimation	Adaptive seamless phase II/III trial design			Biomarker-adaptive design
	Multiple adaptive	Multiple adaptive design			Multi-arm multi-stage (MAMS)

Second, the data were classified using clinicaltrials.gov, a clinical trial registry; however, in some cases, information about which adaptive designs were used was not fully provided. In addition, in cases of clinical trials that were stopped owing to a lack of subjects or technical issues, I could not access detailed information; thus, I classified these cases as the 'Unknown' category. Therefore, the possibility of an unidentified adaptive design in addition to a clearly identified adaptive design cannot be ruled out.

Finally, only the cases retrieved through the search keywords obtained from the FDA guidelines were identified, and there is a possibility that other adaptive design cases exist in addition to the corresponding results. However, our research classified the results retrieved by the set standards according to indication types, phases, and adaptation methods, and through the results, the current status of adaptive design was updated.

Chapter 5. Conclusion

In this study, I highlighted the current status of adaptive design, considerations for its use, and its application in various indication types and phases. In addition, I analyzed COVID-19 clinical trial cases to gain insight into designing adaptive clinical trials in a pandemic situation. I expect that our findings can offer valuable perspectives and considerations for researchers and clinical trial data reviewers to apply appropriate adaptive designs depending on the situation of the clinical phase and indication types in the future.

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Supplementary Informations

Supplementary Table 1. Number of cases using multiple adaptive design in infectious disease clinical trial by phase

Infectious disease	Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Total
Seamless phase	0	4	0	8	0	12 (33.3)
Adaptive treatment selection	3	2	4	2	0	11 (30.6)
Group sequential design	0	0	0	3	3	6 (16.7)
Adaptive sample size re-estimation	1	0	1	1	0	3 (8.3)
Unknown	1	0	0	0	1	2 (5.6)
Adaptive randomization design	0	0	0	1	0	1 (2.8)
Adaptive hypothesis design	0	0	0	1	0	1 (2.8)
Adaptive sub-population analysis	0	0	0	0	0	0 (0)

Supplementary Table 2. Number of cases using multiple adaptive design in neurologic clinical trial by phase

Neurologic	Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Total
Adaptive treatment selection	5	3	14	3	0	25 (48.1)
Seamless phase	0	5	0	4	0	9 (17.3)
Group sequential design	1	0	3	0	2	6 (11.5)
Adaptive randomization design	0	0	4	0	2	6 (11.5)
Adaptive sample size re-estimation	0	0	2	0	0	2 (3.8)
Adaptive sub-population analysis	1	0	1	0	0	2 (3.8)
Unknown	0	0	2	0	0	2 (3.8)
Adaptive hypothesis design	0	0	0	0	0	0 (0)

Supplementary Table 3. Number of cases using multiple adaptive design in autoimmune/inflammatory disease clinical trial by phase

Autoimmune/inflammatory	Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Total
Adaptive treatment selection	1	2	10	2	0	15 (37.5)
Seamless phase	0	4	0	3	0	7 (17.5)
Adaptive randomization design	0	1	4	0	1	6 (15.0)
Unknown	3	0	2	0	0	5 (12.5)
Group sequential design	1	1	0	1	1	4 (10.0)
Adaptive sample size re-estimation	0	0	2	0	0	2 (5.0)
Adaptive sub-population analysis	1	0	0	0	0	1 (2.5)
Adaptive hypothesis design	0	0	0	0	0	0 (0.0)
Adaptive treatment selection	1	2	10	2	0	15 (37.5)

Supplementary Table 4. Number of cases using multiple adaptive design in metabolic/endocrinology disease clinical trial by phase

Metabolic/endocrinology	Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Total
Adaptive treatment selection	5	2	1	1	0	9 (40.9)
Seamless phase	0	3	0	2	0	5 (22.7)
Group sequential design	1	1	0	0	0	2 (9.1)
Adaptive randomization design	0	0	1	0	1	2 (9.1)
Unknown	1	0	1	0	0	2 (9.1)
Adaptive sample size re-estimation	0	0	1	0	0	1 (4.5)
Adaptive sub-population analysis	1	0	0	0	0	1 (4.5)
Adaptive hypothesis design	0	0	0	0	0	0 (0.0)

Supplementary Table 5. Number of cases using multiple adaptive design in cardiovascular disease clinical trial by phase

Cardiovascular	Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Total
Adaptive treatment selection	1	1	2	1	0	5 (27.8)
Adaptive randomization design	0	0	1	0	3	4 (22.2)
Group sequential design	0	0	0	0	3	3 (16.7)
Seamless phase	0	2	0	1	0	3 (16.7)
Adaptive sample size re-estimation	0	1	0	0	1	2 (11.1)
Unknown	0	0	1	0	0	1 (5.6)
Adaptive sub-population analysis	0	0	0	0	0	0 (0.0)
Adaptive hypothesis design	0	0	0	0	0	0 (0.0)

Supplementary Table 6. Number of cases using multiple adaptive design in respiratory disease clinical trial by phase

Respiratory	Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Total
Group sequential design	2	0	3	0	0	5 (45.5)
Adaptive treatment selection	1	0	1	0	1	3 (27.3)
Adaptive sample size re-estimation	0	0	1	0	0	1 (9.1)
Adaptive sub-population analysis	0	0	1	0	0	1 (9.1)
Unknown	0	0	1	0	0	1 (9.1)
Adaptive randomization design	0	0	0	0	0	0 (0.0)
Adaptive hypothesis design	0	0	0	0	0	0 (0.0)
Seamless phase	0	0	0	0	0	0 (0.0)

Supplementary Table 7. Number of cases using multiple adaptive design in healthy subject clinical trial by phase

Healthy	Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Total
Adaptive treatment selection	6	0	0	0	0	6 (66.7)
Group sequential design	1	0	0	0	0	1 (11.1)
Adaptive randomization design	1	0	0	0	0	1 (11.1)
Adaptive hypothesis design	1	0	0	0	0	1 (11.1)
Adaptive sample size re-estimation	0	0	0	0	0	0 (0.0)
Adaptive sub-population analysis	0	0	0	0	0	0 (0.0)
Seamless phase	0	0	0	0	0	0 (0.0)
Unknown	0	0	0	0	0	0 (0.0)

Supplementary Table 8. Number of cases using multiple adaptive design in other indication clinical trial by phase

Other indications	Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Total
Adaptive treatment selection	1	1	6	1	0	9 (40.9)
Group sequential design	1	0	0	1	3	5 (22.7)
Seamless phase	0	1	0	2	0	3 (13.6)
Adaptive randomization design	0	0	0	0	2	2 (9.1)
Unknown	0	0	0	0	2	2 (9.1)
Adaptive sample size re-estimation	0	0	0	0	1	1 (4.5)
Adaptive sub-population analysis	0	0	0	0	0	0 (0.0)
Adaptive hypothesis design	0	0	0	0	0	0 (0.0)

Abstract (Korean)

서론: 적응성 임상시험 디자인은 임상시험 진행 중 미리 계획되어 있는 중간 분석에 따라 구조화된 계획을 변경할 수 있는 디자인이다. 이 방법은 일반적인 임상시험보다 성공률을 높이고 시간, 비용, 샘플 크기를 줄일 수 있다. 본 연구의 목적은 적응형 디자인 적용 사례의 현황을 파악하고, 적응증 및 임상시험 단계별 적응형 디자인의 설계 개요를 제공하며, 특정 상황에 따라 적절한 적응형 디자인을 계획하기 위한 주요 고려 사항을 제시하는 것이다.

방법: FDA 적응성 임상시험 디자인에 대한 가이드라인에서 키워드를 추출하여 임상시험 레지스트리(Clinicaltrials.gov)에서 검색을 진행하였다. 각 임상시험 단계 및 적응증 유형에서 사용된 적응적 디자인을 분석, 비교하기 위해 검색결과를 각 임상시험 단계, 적응증 유형 및 적응적 디자인의 종류에 따라 분류하였다.

결과: Clinicaltrials.gov 에서 총 267 건의 임상 시험이 검색되었으며 이 중 적응적 디자인이 실제로 적용된 236 건의 임상시험을 임상시험 단계, 적응증 유형, 적응설계 유형에 따라 분류했다. 적응적 디자인은 2 상 임상시험과 종양학 연구에서 가장 많이 사용되었으며. 가장 일반적으로 사용되는 적응적 디자인은 적응적 치료군 선택 디자인이었다. 추가적으로 진행된 코로나 19 임상시험의 적응적 플랫폼 디자인과 심리스 디자인이 가장 많이 사용되었다.

결론: 본 연구는 적응성 임상시험의 최신 동향을 강조하며, 다양한 질병과 단계에 적응성 임상시험을 적용하는 데 있어서 유익한 시각과 고려 사항을 제공할 것으로 예상된다. 결과적으로 본 연구의 결과를 통해 향후 임상시험 수행 연구자가 적절한 적응적 디자인을 사용하는 데에 가치 있는 시각과 고려 사항을 제공할 수 있을 것으로 기대된다.

주요어: 적응적 임상시험, 중간 분석, 유연성, 샘플 크기 감소, 비용 효율성, 프로토콜 수정

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