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Original Article

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Adaptive design clinical trials: current status by disease and trial phase in various perspectives

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ABSTRACT

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. We 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 Adaptive Design Clinical Trial Guidelines. In order to analyze the adaptive designs used in selected cases, we classified the results according to the phase of the clinical trial, type of indication, and the specific adaptation method employed. 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 coronavirus disease 2019, the most frequently used designs were adaptive platform design and seamless design. Through this study, we expect to provide valuable insights and considerations for the implementation of adaptive design clinical trials in different diseases and stages.

Keywords: Adaptive Clinical Trial Design; Early Termination of Clinical Trials; Flexibility; Cost Effectiveness; Data Adjustment; Bayesian Analysis

INTRODUCTION

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.

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Author Contributions

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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 [2,3]. However, there are limitations and disadvantages, owing to a modification in the direction favorable to the clinical trial objectives such as type 1 error, that must be considered when designing an adaptive design. 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 [4].

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 [5]. 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 [6].

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 [6-10]: 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. The definition of each adaptive design in this study are represented in **Table 1** [5-7,11-15].

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 [5,16,17]. In addition, the studies analyzing the adaptive design clinical trials did not include phase 1 and 1/2, owing to the low impact on regulatory approvals despite their role in drug development [16,17].

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.

METHODS

Data source and search strategy

We summarized ongoing or terminated clinical trials with adaptive design from the clinical trial registry "ClinicalTrials.gov" from January 2006 to July 2021. We searched for clinical trials using several keywords as follows 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; "adaptive design," "flexible design," "adaptive trial," "adaptive method," "adaptive dose adjusting," "adaptive allocation," "sample size

Table 1. Definitions of types of adaptive designs

Type of adaptive design	Definition
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 [5]. In group sequential design, 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.
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-adaptive randomization which is a method of randomly assigning subjects to treatment groups based on the cumulative results of the baseline characteristics of the previously enrolled subjects and randomization ratio and response-adaptive randomization which determines a new randomization ratio based on the results of previously enrolled subjects using interim analysis [5,12,13].
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 sample size re-estimation	An adaptive sample size re-estimation 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 [5,14]. By using an adaptive sample size reestimation design, such problems can be prevented.
Adaptive dose finding design	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.
Adpative hypothesis 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 [5]. 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 [6].
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.
Seamless phase 2/3 design	Seamless phase 2/3 design combines two different phases, that is, the learning and confirmatory phases, into a single clinical trial [7,15]. In a seamless phase 2/3 design, the exploratory and confirmatory phases are integrated and proceed to phase 3 by adding more patients to a specific treatment group or by extending the follow-up period while remaining in phase 2 clinical trials. The most efficacious dose group was observed in phase 2, and the effect of the dose group followed immediately to phase 3. In this design, the inclusion/exclusion criteria of the enrollment or randomization scheme remain unchanged [15].

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." The document describes important principles for designing, conducting, and reporting the results from adaptive design clinical trials. The retrieved results were confirmed to determine whether adaptive design was actually used, as included in our pre-determined adaptive design categories.

Data analysis

The retrieved results were classified based on the phases (phase 1/2/3), 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, we checked the first posted year of each cases in the registry to confirmed the trend of adaptive design by year until the latest case.

We have reviewed the study summaries from the ClinicalTrials.gov registry to determine the adaptive design used 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, we classified these as 'Unknown.'

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Regarding the use of multiple adaptive designs in cases, we 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.

Additionally, we have also analyzed the adaptive design used in clinical trials of biotherapeutic products, a biologically derived medication, often using proteins, antibodies, or nucleic acids, which have been getting attention in the field of drug development recently. We examined the intervention/treatment section in the registry to identify the name or code of the drug and to determine whether it was a biotherapeutic drug, and assessed the types of adaptive designs that were employed.

Lastly, we specifically identified the adaptive methods used in coronavirus disease 2019 (COVID-19) cases to confirm the application of adaptive design in a pandemic situation. Based on this data, we intend to present key considerations for the application of adaptive design in potential future pandemic situations.

RESULTS

Search results

A total of 267 clinical trials conducted through July 2021 were identified on ClinicalTrials.gov using predetermined keywords from FDA guidance. Brief summaries and detailed descriptions were checked in the registry of each case to classify which adaptive design was used, as well as accessible documents to specify the study design. We collected and analyzed only those instances where the precise utilization of adaptive design was explicitly stated in the respective documents and registry information, or when its usage was confirmed within the reviewed research documents. As a result, we analyzed 236 trials in which the adaptive design was actually implemented out of 267 trials. The total number of adaptive designs used was 292, in 236 trials. The most commonly used adaptive design was the adaptive treatment selection design with 110 (37.7%) out of 292 trials. This was followed by the seamless phase design, which was used in 56 (19.2%) trials, and the group sequential design, which was used in 49 (16.8%) trials (**Table 2**).

In analyzing clinical trials that utilized 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 (**Fig. 1**).

Table 2. Most frequently used adaptive design in all clinical trials

Types of adaptation methods	Number of adaptive design used (%)
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 number	292 (100.0)

Data are displayed as number of adaptive design used (percentage of adaptive design used).
Percentages are based on the total number of adaptive design used in all cases.
*When the type of adaptive design used in trial was unknown due to limited information on registry, we classified these as 'Unknown.'

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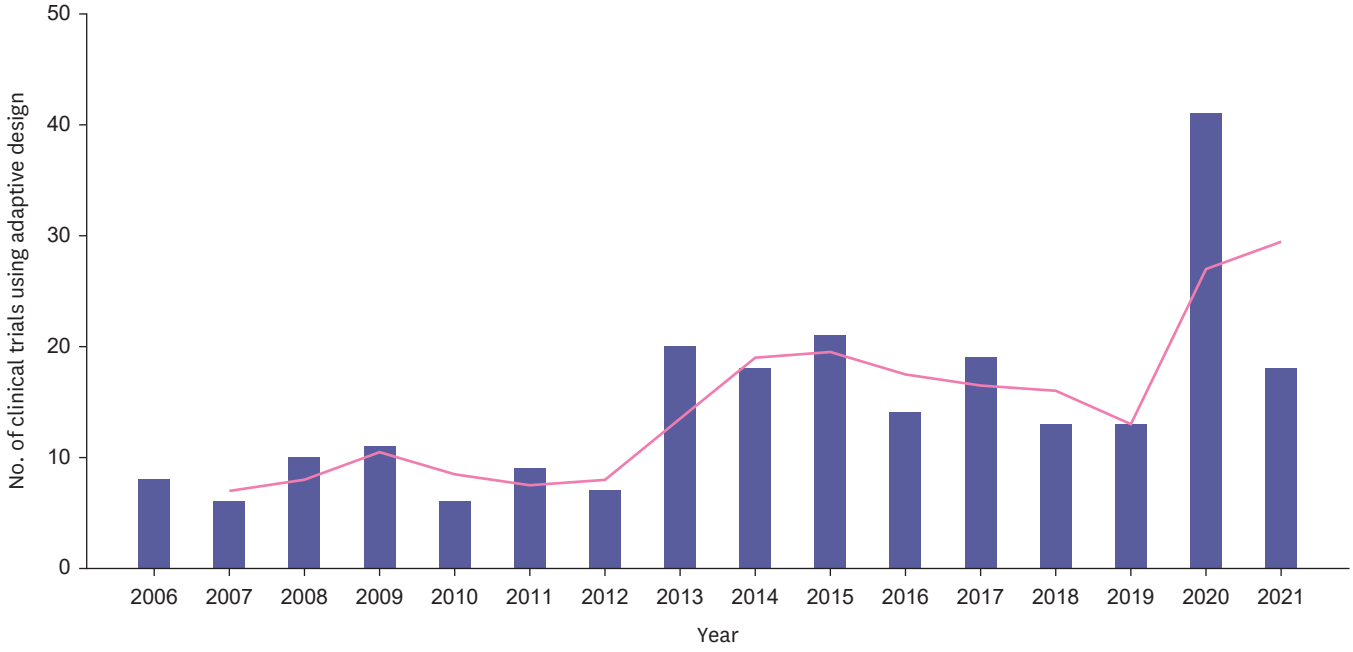

Figure 1. Annual statistics of clinical trial using adaptive design. Number of adaptive design clinical trials by year: It has been confirmed that the average number of cases of adaptive design clinical trials per year has shown a gradual increasing trend, particularly in 2020 with 41 cases.

Adaptive design by phases

As a result of classifying a total of 292 adaptive design clinical trials by phase, it was found that adaptive design was most frequently used in phase 2 clinical trials. Specifically, adaptive designs were used in 97 (41.1%) trials out of 236 trials used in phase 2, used in 48 (20.3%) trials in phase 1, used in 35 (14.8%) trials in phase 3, used in 29 (12.3%) trials in phase 2/3, and used in 27 (11.4%) trials in phase 1/2 (**Fig. 2**). In the case of phase 1/2 and phase 2/3

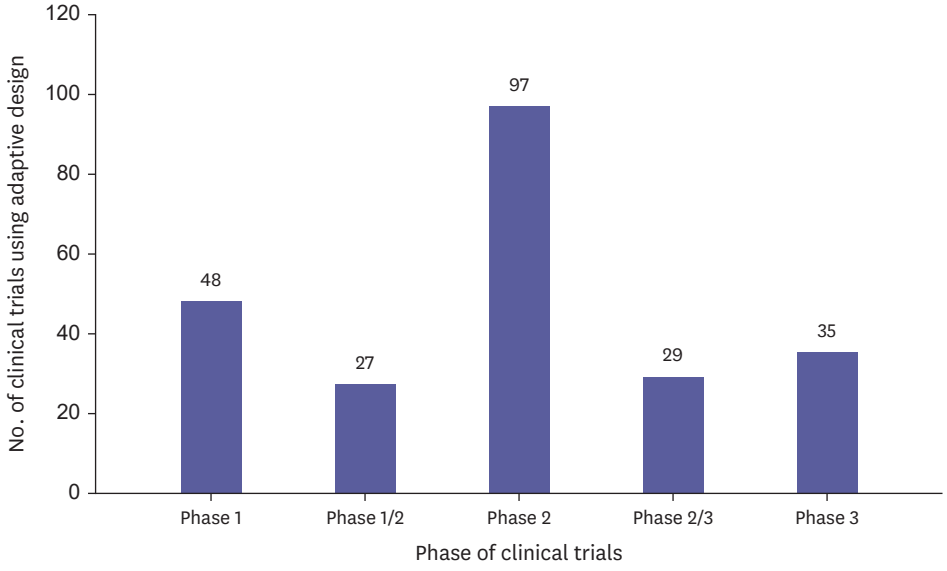

Figure 2. Number of clinical trials using adaptive design by phase. Number of clinical trial using adaptive design: phase 2 clinical trials had the highest frequency of adaptive design use, with 97 cases identified. This was followed by phase 1 trials with 48 cases, and phase 2/3 trials with 29 cases. 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.

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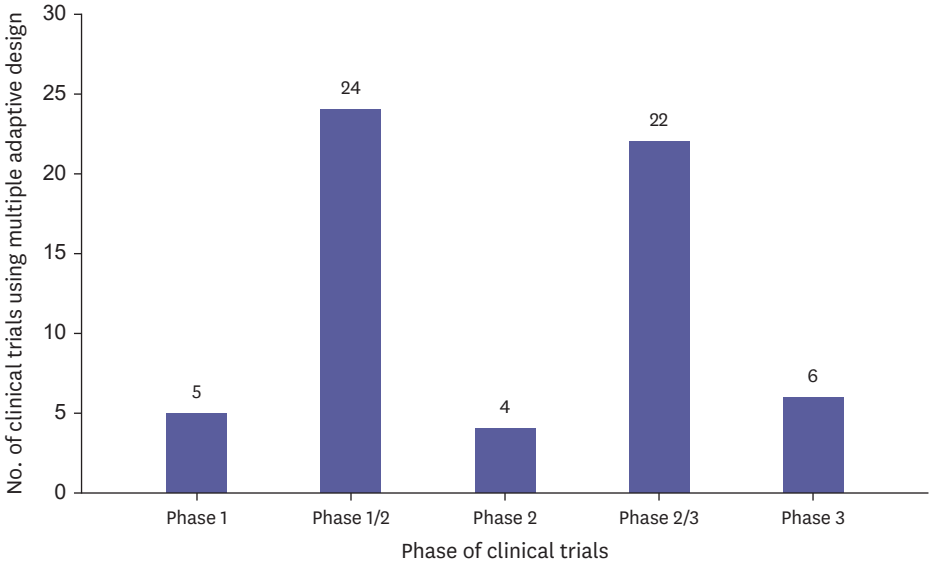

Figure 3. Number of clinical trials using multiple adaptive design by phase. Number of clinical trials applying multiple adaptive designs: All cases of phase 1/2 and phase 2/3 confirmed the use of seamless phase design, resulting in the incorporation of multiple adaptive features into a single clinical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

clinical trials, most trials were analyzed using a multiple adaptive design because all trials were designed in a seamless phase design (**Fig. 3**).

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 3**). Seamless phase design was the most commonly used design in phase 1/2 and phase 2/3 clinical trials. Excluding seamless phase design, the adaptive treatment selection design was used the most, same as phase 1 and phase 2.

Adaptive designs by indication types

A total of 292 adaptive designs used were classified by indication types. As a result, it was found that adaptive design was most frequently used in oncology clinical trials. Specifically, adaptive designs were used in 62 (26.3%) oncology disease trials out of 236 trials, used in 43 (18.2%) neurology trials, used in 32 (13.6%) autoimmune/inflammatory diseases trials, used in 32 (13.6%) infectious disease trials, used in 18 (7.6%) metabolic/endocrinology disease trials, used in 14 (5.9%) cardiovascular disease trials, used in 10 (4.2%) respiratory disease trials, used in 8 (3.4%) healthy subjects trials, and used in 17 (7.2%) trials for other

Table 3. Most frequently used adaptive designs by phase

Phase	Number of clinical trials that used adaptive designs	Most frequently used adaptation methods	Number of clinical trials using the most frequently used adaptation methods (%)
Phase 1	48	Adaptive treatment selection	33 (68.8)
Phase 1/2	27	Seamless phase design	27 (100.0)
Phase 2	97	Adaptive treatment selection	44 (45.4)
Phase 2/3	29	Seamless phase design	29 (100.0)
Phase 3	35	Group sequential design	21 (60.0)
Total number	236		

Data are displayed as number of clinical trials (percentage).
Percentages are calculated based on the number of clinical trials using the most frequently used adaptation methods divided by the total number of clinical trials that used adaptive design within each phase.

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indications (**Fig. 4**). 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 4**). 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 trials 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

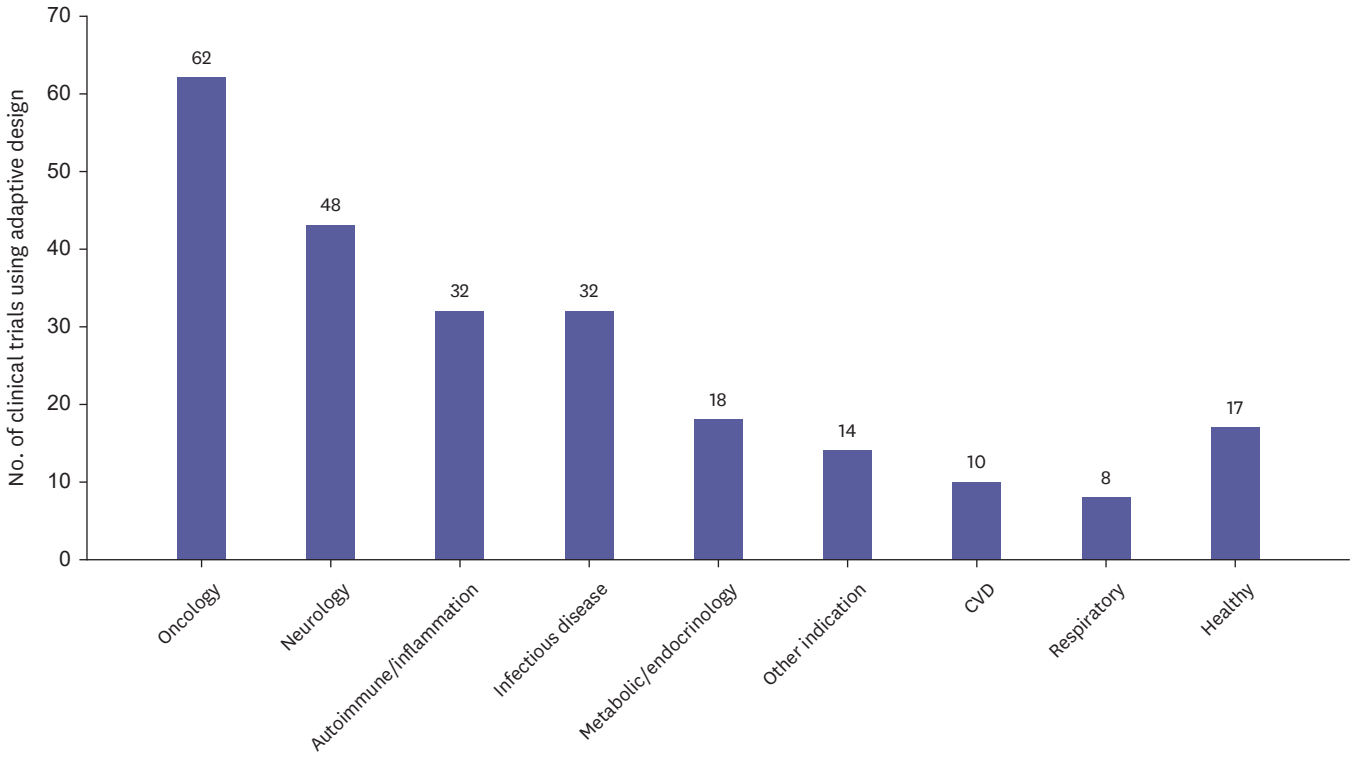

Figure 4. Number of clinical trials using adaptive design by indication types. Number of clinical trials using adaptive design by indication type: oncology clinical trials showed the highest frequency of adaptive design use with 62 cases, followed by neurology with 48 cases, and autoimmune/inflammatory disease and infectious disease with 32 cases, respectively. Most of the adaptive designs were used in clinical trials involving patients, while they were least utilized in clinical trials involving healthy subjects.
CVD, cardiovascular disease.

Table 4. Most frequently used adaptive designs by indication types

Indication types	Number of clinical trials that used adaptive designs	Most frequently used adaptation methods	Number of clinical trials using the most frequently used adaptation methods (%)
Neurology	43	Adaptive treatment selection	25 (58.1)
Oncology	62	Adaptive treatment selection	25 (40.3)
Autoimmune/ inflammation	32	Adaptive treatment selection	15 (46.9)
Infectious disease	32	Seamless phase design	12 (37.5)
Metabolic/endocrinology	18	Adaptive treatment selection	9 (50.0)
Healthy	8	Adaptive treatment selection	6 (75.0)
Cardiovascular disease	14	Adaptive treatment selection	5 (35.7)
Respiratory disease	10	Adaptive treatment selection	5 (50.0)
Total number	219*		

Data are displayed as number of clinical trials (percentage).
Percentages are calculated based on the number of clinical trials using the most frequently used adaptation methods divided by the total number of clinical trials that used adaptive design within each phase.
*Total number of clinical trials using adaptive design except for 'Other indications' category.

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Table 5. Number of adaptive designs in oncology disease clinical trials by phase

Oncology	Phase 1	Phase 1/2	Phase 2	Phase 2/3	Phase 3	Number of adaptive design used (%)
Adaptive treatment selection	9	7	4	3	2	25 (40.3)
Group sequential design	1	0	8	2	8	19 (30.6)
Seamless phase	0	8	0	9	0	17 (27.4)
Adaptive randomization design	0	0	8	1	0	9 (14.5)
Adaptive sample size re-estimation	0	0	1	1	2	4 (6.5)
Adaptive sub-population analysis	0	0	3	0	1	4 (6.5)
Unknown*	1	0	3	0	0	4 (6.5)
Adaptive hypothesis design	0	0	0	0	0	0 (0.0)
Total number of oncology clinical trials using adaptive design						62 (100.0)

Data are displayed as number of adaptive design used in oncology clinical trials (percentage of adaptive design used in oncology clinical trials).
Percentages are based on the total number of oncology clinical trials using adaptive design.
*When the type of adaptive design used in trial was unknown due to limited information on registry, we classified these as 'Unknown.'

phase 2/3 was adaptive treatment selection design, similar to phase 1 trials (**Table 5**). For statistics on other indication types by phase are presented in the **Supplementary Tables 1-8**.

Regarding to biotherapeutic drug clinical trials, there were 51 clinical trials investigating biotherapeutic products in the dataset. According to the results, a total of 66 adaptive designs were employed. Notably, the most frequently utilized adaptive design in clinical trials for biotherapeutic drugs was the adaptive treatment selection design, which was employed in 24 out of the 51 trials (47.1%). This was followed by the seamless phase design, used in 16 trials (31.4%), and the adaptive randomization design, employed in 10 trials (19.6%) (**Table 6**).

Adaptive designs in COVID-19 clinical trial

To validate the findings of adaptive design in COVID-19 clinical trials, we conducted an additional analysis specifically focusing on COVID-19 clinical trials within the category of infectious disease. There were a total of 25 adaptive designs used in 16 COVID-19 clinical trials. Specifically, there were 9 (56.3%) COVID-19 trials using adaptive platform design, which was used the most, out of 16 trials. This was followed by seamless phase design, which was used in 8 (50.0%) trials, and group sequential design, which was used in 3 (18.8%) trials (**Table 7**).

DISCUSSION

An adaptive design clinical trial design adds flexibility to conventional clinical trials by allowing changes in the planned protocol based on the results accumulated during the

Table 6. Number of adaptive designs in biotherapeutic drug clinical trial

Adaptive design	Number of biotherapeutic drug clinical trials (%)
Adaptive treatment selection	24 (47.1)
Seamless phase	16 (31.4)
Adaptive randomization design	10 (19.6)
Group sequential design	8 (15.7)
Adaptive sample size re-estimation	3 (5.9)
Unknown*	3 (5.9)
Adaptive sub-population analysis	2 (3.9)
Adaptive hypothesis design	0 (0)
Total number of clinical trials using adaptive design	51 (100.0)

Data are displayed as number of adaptive design used in biotherapeutic drug cases (percentage of adaptive design used in biotherapeutic drug cases).
Percentages are based on the total adaptive design used in biotherapeutic drug cases.
*When the type of adaptive design used in trial was unknown due to limited information on registry, we classified these as 'Unknown.'

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Table 7. Number of adaptive designs in COVID-19 clinical trial

Adaptive design	Number of COVID-19 clinical trials (%)
Adaptive platform design	**9 (56.3)**
Seamless phase	8 (50.0)
Group sequential design	3 (18.8)
Adaptive treatment selection	2 (12.5)
Adaptive sample size re-estimation	1 (6.3)
Adaptive randomization design	1 (6.3)
Adaptive hypothesis design	1 (6.3)
Adaptive sub-population analysis	0 (0.0)
Unknown*	0 (0.0)
Total number of clinical trials using adaptive design	16 (100.0)

Data are displayed as number of adaptive design used in COVID-19 cases (percentage of adaptive design used in COVID-19 cases).
Percentages are based on the total adaptive design used in COVID-19 cases.
COVID-19, coronavirus disease 2019.
Bold font indicates the most used adaptive design in COVID-19 cases.
*When the type of adaptive design used in trial was unknown due to limited information on registry, we classified these as 'Unknown.'

interim analysis. Through these features, adaptive design could offer advantages in reducing the risk and saving the costs and resources which leads to accelerate the decision making for drug development. For example, one of the clinical trials in our study results demonstrated the clear advantages of using an adaptive design. The trial was a phase 2/3 seamless clinical trial aimed at determining the optimal dose of a TRPV1 antagonist for osteoarthritis patients, using a group sequential design with futility criteria [18]. Initially planned for 520 patients, the trial conducted an interim analysis for futility after treating 175 patients for two weeks. The results of interim analysis showed that the investigational drug did not lead to a significant reduction in pain based on the primary variable. As a result of the interim analysis, it was recommended to terminate the trial due to futility. By terminating the trial early based on futility criteria, they were able to save costs and resources for future studies and prevent further exposure of patients to an ineffective investigational drug, a benefit not achievable with traditional clinical trial designs.

In this study, we evaluated the frequency of each adaptive design used across different diseases and phases, provided an updated overview, and suggested considerations when designing future adaptive design clinical trials based on specific indications and clinical trial phases.

A total of 236 clinical trials 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 instances of usage, followed by 56 of seamless phase design.

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 design 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 110 adaptive treatment selection designs, in most cases, 96 trials used an adaptive dose-finding design in phase 1, 1/2, and 2 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 trials. 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 3 clinical trials, the group sequential design was used most frequently, used in 21 (60.0%) trials out of 35 phase 3 trials. Because phase 3 clinical trials require a large number of subjects, high cost, and time compared to phase 1 and II trials, this phase mainly 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 oncology diseases (used in 62 trials), followed by 48 trials for neurology, and 32 trials for autoimmune/inflammatory disease. In the oncology and neurology clinical trials, there were 134 clinical trials using adaptive design out of 236 trials.

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 [19]. Accordingly, among the adaptive designs used in oncology clinical trials, adaptive treatment selection design was the most common, used in 25 trials, followed by group sequential design, with 19 trials using it.

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 [20]. As a result, adaptive platform design was the most commonly used in 9 (56.3%) trials, 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, a multistage adaptive platform protocol for rapid vaccine development since the emergence of COVID-19 developed by Stanford University [21], is an example of a platform design, and 3 trials 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.

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There were also 8 trials (50.0%) of using 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 trials in this study, we conceived a schematic of adaptive design in a pandemic situation to suggest considerations for future researchers (**Fig. 5**).

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 2. 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.

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 we 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 8**).

Table 8. 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 2/3 trial design			Biomarker-adaptive design
	Multiple adaptive	Multiple adaptive design			Multi-arm multi-stage (MAMS)

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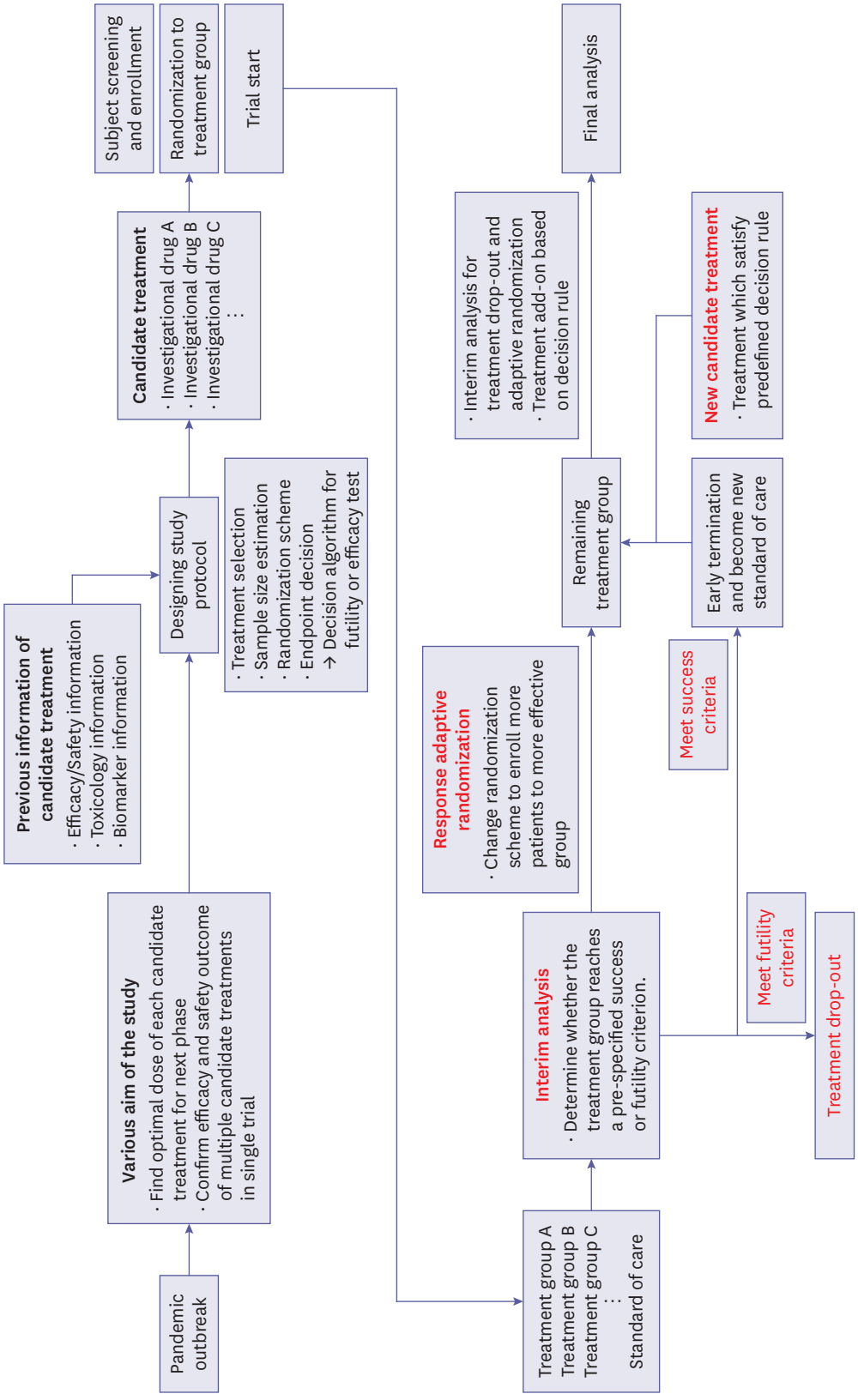

Figure 5. Adaptive design recommendation scheme for future pandemic situation. Schematic of adaptive design that can be used in new infectious diseases such as coronavirus disease 2019. The part indicated in red in the corresponding schematic is the part to which the adaptive design features are applied.

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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, we could not access detailed information; thus, we 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.

In this study, we highlighted the current status of adaptive design, considerations for its use, and its application in various indication types and phases. In addition, we analyzed COVID-19 clinical trials to gain insight into designing adaptive design clinical trials in a pandemic situation. We 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.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Number of adaptive designs in infectious disease clinical trials by phase

Click here to view

Supplementary Table 2
Number of adaptive designs in neurologic disease clinical trials by phase

Click here to view

Supplementary Table 3
Number of adaptive designs in autoimmune/inflammatory disease clinical trials by phase

Click here to view

Supplementary Table 4
Number of adaptive designs in metabolic/endocrinologic disease clinical trials by phase

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Supplementary Table 5
Number of adaptive designs in cardiovascular disease clinical trials by phase

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Supplementary Table 6

Number of adaptive designs in respiratory disease clinical trials by phase

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Supplementary Table 7

Number of adaptive designs in clinical trials with healthy subjects by phase

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Supplementary Table 8

Number of adaptive designs in clinical trials with other indications by phase

Click here to view

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