The distribution characteristics and regulations of adaptive designs from 2008 to 2020: an overview of EMA approvals

Xiaowei Huang[1], Jianbin Ma[2], Zhenzhen Lu[1], and Lihong Huang[1]

[1]Zhongshan Hospital Fudan University
[2]Chengdu University of Information Technology

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Abstract

Objective: To identify and characterize all European Medicines Agency (EMA) approvals that made use of adaptive designs in clinical trials and to evaluate the conditions where adaptive designs were required. Methods: We gathered relevant files derived from the EMA database based on a list of the keywords related to adaptive designs between 2008 and 2020. We collected the trial characteristics from approvals and Fisher exact test was used to compare the characteristics. Results: We found 41 approvals derived from 91 original EMA files contained adaptive designs. Group sequential was the most popular adaptive design (17/41). Most of the approvals (32/41) were pivotal trials and were not under accelerated assessment (38/41). Among 32 confirmatory trials planned with adaptive designs, the proportion of AM status showed a statistically significant increase (P < 0.0001) from 0% in 2008–2012 to 90.48% in 2017–2020. The percentage of antitumor drugs in approved drugs with ongoing clinical trials was 82.35%, compared to 20.83% with completed trials (P=0.0001). The proportion of companies that required post-authorization safety or efficacy studies or that were granted CMA for drugs that were approved but still had ongoing clinical trials significantly differed from the other group (P = 0.0230). Conclusion: An increasing trend was observed in the number of EMA approvals related to adaptive designs from 2008 to 2020. Extra regulations will be necessary for ongoing trials due to unknown, uncertain circumstances raised from adaptive design, such as addtitonal monitoring, conditional marketing authorization.

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Xiaowei Huang[1], Jianbin Ma[3], Zhenzhen Lu[1,2+], Lihong Huang[1,2+]

[1]Zhongshan Hospital, Fudan University, Shanghai, China, 200032.

[2]Institute of Clinical Science, Zhongshan Hospital of Fudan University, Shanghai, China, 200032.

[3]Chengdu University of Information Technology, Chengdu, China.

[+]Corresponding authors:

Zhenzhen Lu, Fenglin Road 180, Xuhui District, Shanghai, China; telephone: 86-021-64041990; email: lu.zhenzhen@zs-hospital.sh.cn

Dr. Lihong Huang; Fenglin Road 180, Xuhui District, Shanghai, China; telephone: 86-021-64041990; email: huang.lihong@zs-hospital.sh.cn

ABSTRACT

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Results : We found 41 approvals derived from 91 original EMA files contained adaptive designs. Group sequential was the most popular adaptive design (17/41). Most of the approvals (32/41) were pivotal trials and were not under accelerated assessment (38/41). Among 32 confirmatory trials planned with adaptive designs, the proportion of AM status showed a statistically significant increase ($P < 0.0001$) from 0% in 2008–2012 to 90.48% in 2017–2020. The percentage of antitumor drugs in approved drugs with ongoing clinical trials was 82.35%, compared to 20.83% with completed trials (P =0.0001). The proportion of companies that required post-authorization safety or efficacy studies or that were granted CMA for drugs that were approved but still had ongoing clinical trials significantly differed from the other group ($P = 0.0230$).

Conclusion : An increasing trend was observed in the number of EMA approvals related to adaptive designs from 2008 to 2020. Extra regulations will be necessary for ongoing trials due to unknown, uncertain circumstances raised from adaptive design, such as addtitonal monitoring, conditional marketing authorization.

KEYWORDS:

Adaptive design; drug approval; EMA; adverse drug reaction

Introduction

The cost of drug development has risen dramatically in recent decades. Even so, the rising costs of clinical trials have not contributed to a higher success rate in approval. For instance, as recorded by BioMedTracker, for 4275 clinical trials that released their results from 2003 to 2010, the overall success rate for final approval of the trial drug or intervention was only 9% [1]. Some factors that may be contributing to the low success rate include the enactment of more regulations and laws concerning medicines. Factors such as the complexity of the health insurance system and the limit to using original biological technology in trials often add to the costs of trials. In traditional clinical trials, a long time is needed to recruit and follow up with patients during the development of medicines. Conventionally, the duration of phase II is more than 18 months, while phase III lasts for another 2 years after that [2]. To address this problem, much thought has been given to ways to reduce the cost of drug development and increase the efficiency of study designs without compromising the integrity and validity of the development.

In 1989, Bauer [3] initially proposed an confirmatory methodology in "Multistage testing with adaptive designs", which allowed multistage design modifications in ongoing trials without compromising on the type I error rate. In contrast to traditional clinical trials, studies planned with adaptive design allow for prospectively design modifications on one or more aspects of the design—such as sample size, randomization ratio, number of treatment arms—on the basis of accumulating data from patients in the trial at an interim analysis with full control of the type I error.

Originally, the most popular adaptive design was sample size re-estimation. The release of regulatory guidance documents in Europe [4] and the United States [5] further expedited the development of adaptive designs. According to a survey of scientific advice letters from the European Medicines Agency (EMA), Elsäßer et al. concluded an overall positive opinion for the majority of proposed adaptive clinical trials [6]. However, according to the EMA guidance, the adoption of adaptive designs should be undertaken with caution. The most frequent concerns raised by the Committee for Human Medicinal Products (CHMP)/Scientific Advice Working Party (SAMP) were insufficient justifications for the adaptation strategy, type I error rate control, and bias [6].

Considering the increasing interest in adaptive design, the question arises as to whether the challenges of maintaining the integrity of the adaptive design trial and the safety concerns can impact regulatory decision-making. It is not the intention of this study to discuss specific clinical scheduling issues associated with adaptive design trials but rather to systematically evaluate the role of adaptive design in the regulatory approval process of the EMA by comparing and characterizing all approvals that use adaptive design.

METHODS

Data derivation

For the EMA, for each approved drug, we saved the scientific discussion, label, and/or public assessment report listed in the database. Figure 1 shows a schematic overview of our method. To find candidate documents, we searched for the following terms [5, 7-10]: *adaptive design, group sequential design, seamless design, adaptations to the sample size, sample size re-estimation, adaptations to the patient population, enrichment, adaptations to the treatment arm selection, adaptive dose-ranging, adaptive dose-finding, hypothesis adaptive design, biomarker adaptive design, adaptive treatment switching design, multiple adaptive design, umbrella design, basket design, platform design, adaptations to patient allocation, covariate-adaptive treatment assignment, adaptations to endpoint selection, adaptive randomization method,* and *drop-loser design* . Once at least 1 of these terms occurred in a document, the associated submission package was scanned to determine whether it included terms listed above. These approvals were incorporated into the candidate list.

Data extraction

The resulting list of the included articles/trials was discussed by JBM and LH to ensure the accuracy of the final decision. XWH performed the manual assessment, and, in case of doubt, the assessment was discussed with JBM. A Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) database was used to collect the relevant information on the included trials. We collected all available trial characteristics (Table 1), incorporating the type of file, the status of authorization, the year of authorization, the name of medicine, the orphan designation, the pivotal status, the accelerated assessment status, AM status, CMA, whether it required PASS, whether it required PAES, NAS status, the types of adaptive designs, the therapeutic area, the system organ class (SOC), the antitumor status, the study progression, the study duration, and the sample size from the respective approval. The keyword served as a pivotal cue to locating targeting approvals to distinguish between studies scheduling adaptive designs in confirmatory trials from eligible approvals.

Table1. Definitons of trial characteristics

Trial characteristic	**Definition**
Types of file	It contains public assessment reports, scientific discussions, and product information, all of
Year of authorization	It derived from the date when medical products were granted with the first marketing auth
Orphan designation	It determines whether the medince is designated as an orphan drug that referred to treatm
Pivotal status	It determines whether an adaptive design is scheduled into a confirmatory trial.
Accelerated assessment status	It defines whether the assessment is a rapid assessment of medicines in the centralised proc
AM status	It defines whether the medicine is being monitored closely by regulatory authorities and su
CMA	Medicines granted CMA usually correspond to the interest of public health but with less co
PASS/PAES	It is a study that is carried out after a medicine has been authorized to obtain further infor
NAS status	It defines whether the medicine is a chemical substance not previously authorized as medici
SOC	It is the highest level of the Medical Dictionary for Regulatory Activities (MedDRA) 1 hier
Antitumor status	It depends on whether indications were for cancer diagnosis or treatment.
Study progression	It is derived from the progression of clinical trials at the time when products were approved

Analysis methodology

We used descriptive statistics to describe the dataset, which was divided in 3 time periods (2008–2012, 2013–2016, and 2017–2020) for subgroup summaries. Fisher exact test was used to compare the characteristics among the 3 time periods. Some approvals incorporated ongoing trials planned with adaptive designs at the time the products were approved. We performed additional descriptive statistics by study progressions (approved with ongoing study or completed study) and compared the features using Fisher exact test. To detect a trend over time in the yearly numbers of approvals, we performed joinpoint regression analyses via the Joinpoint Regression Program version 4.7.0.0 (National Cancer Institute and Information Management Services Inc., Bethesda, MD, USA). Other statistical analyses were carried out using SAS version 9.4 (SAS

Institute, Carey, NC, USA). Differences were considered significant based on 2-sided tests if P values were less than 0.05.

Results

During the study period, there were 1759 drugs registered by the EMA. Among them, 1409 were authorized products. In total, 4215 documents incorporating product information, public assessment report, and scientific discussion documents were extracted from the authorized products. A list of keywords on adaptive designs (Table 2) was used to identify 91 documents of interest after 4 duplicated documents were removed [5, 7-10].

Table 2. Definitions of adaptive designs

Type of adaptive designs	**Type of adaptive designs**
Group sequential	Group sequential
Adaptations to the sample size	Adaptations to the sample size
Sample size re-estimation	Sample size re-estimation
Adaptations to the patient population (e.g., adaptive enrichment)	Adaptations to the patient population (e.g., adaptive e
Adaptive dose-ranging	Adaptive dose-ranging
Adaptations to treatment arm selection	Adaptations to treatment arm selection
Seamless design	It addresses study objectives within a single trial that a
Enrichment design	Enrichment design
Basket study	Basket study

A total of 41 approvals with adaptive design trials were identified by manually reviewing and evaluating approvals. Of the 41 approvals, 17 were approved while they still had ongoing trials. The flowchart of the review process is presented in Figure 1.

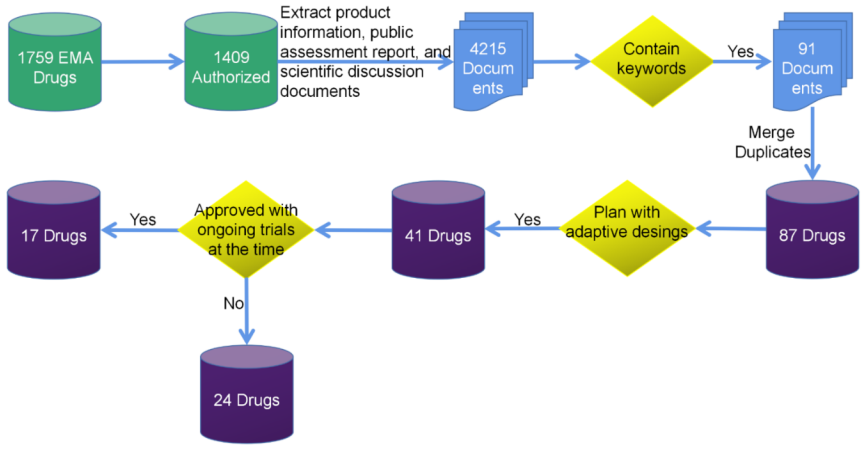

Figure 1. Flowchart of review process

Figure 1. Flowchart of review process

The EMA guidance on adaptive designs was released in 2007 [4]. All eligible approvals were collected after 2007 and divided into 3 periods: 2008–2012, 2013–2016, and 2017–2020. Figure 2 shows that the number of approvals containing different adaptive designs increased over time. Over the past 13 years, the number of approvals related to adaptive designs revealed a significant increasing trend, with a 16.52 Annual Percent Change (APC). The number of approvals containing adaptive design in confirmatory trials also increased significantly, with a 15.54 APC.

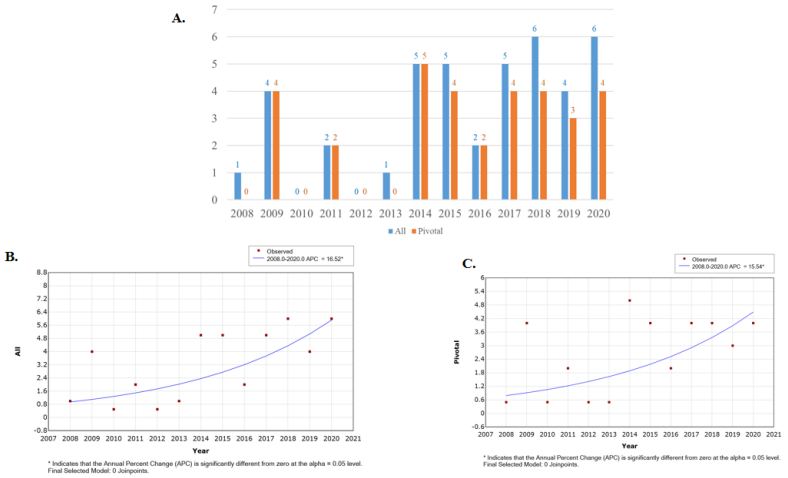

Figure 2. Trends of European Medicines Agency (EMA) approvals with adaptive design trials from 2008 to 2020

Figure 2. Trends of EMA approvals with adaptive design trials from 2008 to 2020

Overall, adaptive designs were mainly composed of group sequential design (17/41, 41.46%) and seamless design (15/41, 36.59%). In the first period, the number of seamless designs was greater than that of group sequential design. From 2013 to 2016, the number of both designs was equal, but the proportion of group sequential design outweighed seamless design between 2017 and 2020. There was also an increase in the diversity of adaptive designs since 2017, which indicated that the planning of design modification had become much more flexible and adaptable (Figure 3).

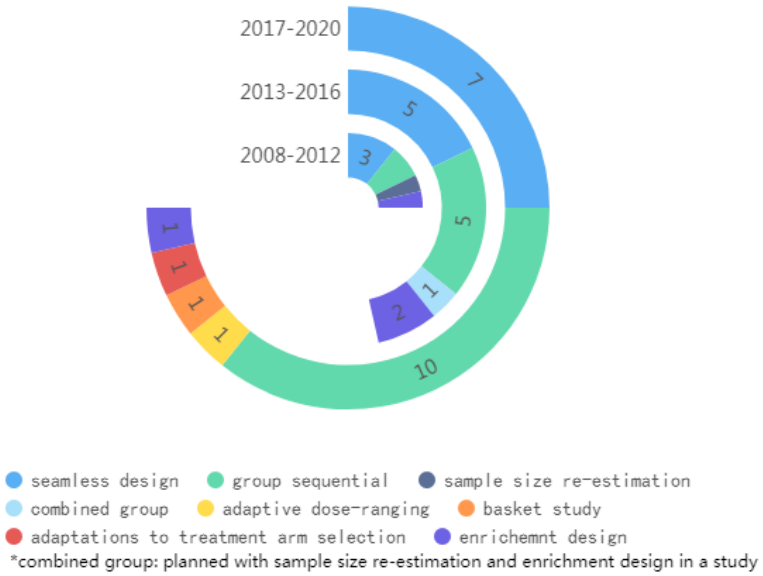

Figure 3. Bar chart of year of first marketing authorization of 41 EMA approvals planned with adaptive designs in clinical trials.

All descriptive statistics in the 3 time periods are reported in Table 3, which provides a general review of

all approvals. Of the 41 approvals, 32 (78.05%) contained an adaptive design trial as pivotal evidence. Most of these were not orphan drug approvals (27/41, 65.85%) but were NAS drug approvals (32/41, 78.05%), and fewer than half were antitumor drug approvals (19/41, 46.34%). Moreover, 92.68% (38/41) were not approved by accelerated assessment, and 53.66% (22/41) were required to undergo AM. Of the 41 products reviewed, 58.54% (24/41) did not require CMA or post-authorisation safety or efficacy studies. In total, approvals including 15 types of indications according to SOC, neoplasms (7/41, 18.92%), and blood system disorders (8/41, 19.51%), were relatively more prevalent. Among the 3 periods, the proportion of AM was the highest in 2017–2020 with statistical significance (Pvalue < 0.0001).

Table 3. Overview of the European Medicines Agency (EMA) approvals planned with adaptive designs

	2008–2012 (n = 7)	**2013–2016 (n = 13)**	**2017–2020 (n = 21)**	**Total (n = 41)**	P **value**[b]
Pivotal trial, n(%)					0.6005
Yes	6 (85.71)	11 (84.62)	15 (71.43)	32 (78.05)	
No	1 (14.29)	2 (15.38)	6 (28.57)	9 (21.95)	
Design types, n(%)					0.7568
Seamless design	3 (42.86)	5 (38.46)	7 (33.33)	15 (36.59)	
Group sequential	2 (28.57)	5 (38.46)	10 (47.62)	17 (41.46)	
Sample size re-estimation	1 (14.29)	0 (0.00)	0 (0.00)	1 (2.44)	
Combined group[a]	0 (0.00)	1 (7.69)	0 (0.00)	1 (2.44)	
Adaptations to treatment arm selection	0 (0.00)	0 (0.00)	1 (4.76)	1 (2.44)	
Adaptive dose-ranging	0 (0.00)	0 (0.00)	1 (4.76)	1 (2.44)	
Basket study	0 (0.00)	0 (0.00)	1 (4.76)	1 (2.44)	
Enrichment design	1 (14.29)	2 (15.38)	1 (4.76)	4 (9.76)	
Orphan drug, n(%)					0.5069
Yes	2 (28.57)	3 (23.08)	9 (42.86)	14 (34.15)	
No	5 (71.43)	10 (76.92)	12 (57.14)	27 (65.85)	
Antitumor drug, n(%)					1.0000
Yes	3 (42.86)	6 (46.15)	10 (47.62)	19 (46.34)	
No	4 (57.14)	7 (53.85)	11 (52.38)	22 (53.66)	
Accelerated assessment, n(%)					0.4110
Yes	1 (14.29)	0 (0.00)	2 (9.52)	3 (7.32)	
No	6 (85.71)	13 (100.00)	19 (90.48)	38 (92.68)	
New active substance, n(%)					0.0912
Yes	4 (57.14)	9 (69.23)	19 (90.48)	32 (78.05)	

No	3 (42.86)	4 (30.77)	2 (9.52)	9 (21.95)	
Additional monitoring, n(%)					**<0.0001**
Yes	0 (0.00)	3 (23.08)	19 (90.48)	22 (53.66)	
No	7 (100.00)	10 (76.92)	2 (9.52)	19 (46.34)	
CMA, PASS, PAES n(%)[c]					0.3286
Yes	3 (42.86)	3 (23.08)	11 (52.38)	17 (41.46)	
No	4 (57.14)	10 (76.92)	10 (47.62)	24 (58.54)	
System organ class indications, n(%)					0.0578
Nervous system disorders	0 (0.00)	1 (7.69)	0 (0.00)	1 (2.44)	
Congenital, familial, and genetic disorders	1 (14.29)	0 (0.00)	1 (4.76)	2 (4.88)	
Renal and urinary disorder	2 (28.57)	0 (0.00)	0 (0.00)	2 (4.88)	
Respiratory, thoracic, and mediastinal disorders	3 (42.86)	1 (7.69)	0 (0.00)	4 (9.76)	
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	1 (14.29)	1 (7.69)	5 (23.81)	7 (18.92)	
Blood and lymphatic system disorders	0 (0.00)	3 (23.08)	5 (23.81)	8 (19.51)	
Gastrointestinal disorders	0 (0.00)	1 (7.69)	3 (14.29)	4 (8.11)	
Skin and subcutaneous tissue disorders	0 (0.00)	1 (7.69)	2 (9.52)	3 (7.32)	
Immune system disorders	0 (0.00)	0 (0.00)	2 (9.52)	2 (4.88)	
Vascular disorders	0 (0.00)	2 (15.38)	0 (0.00)	2 (4.88)	

Metabolism and nutrition disorders	0 (0.00)	1 (7.69)	0 (0.00)	1 (2.44)
Cardiac disorders	0 (0.00)	1 (7.69)	0 (0.00)	1 (2.44)
Infections and infestations	0 (0.00)	1 (7.69)	1 (4.76)	2 (4.88)
Psychiatric disorders	0 (0.00)	0 (0.00)	1 (4.76)	1 (2.44)
Musculoskeletal and connective tissue disorders	0 (0.00)	0 (0.00)	1 (4.76)	1 (2.44)

a: Sample size re-estimation and enrichment design

b: Fisher exact test was conducted

c: Conditional marketing authorisation, Post-authorisation safety study, Post-authorisation efficacy study

Table 4 provides additional descriptive statistics by study progression. Overall, most studies were completed (24/41, 58.54%) before medicines were approved. Group sequential design dominated the majority of design types (9/17, 52.94%) in those drug were approved but ongoing studies continued. In cases in which the drug was approved and studies had been completed, the proportion of seamless design outweighed group sequential design and became the most popular design type (9/24, 37.50%). Compared with the group of products approved with completed studies, the proportion of orphan drugs (8/17, 47.06%) was largely greater. When comparing the 2 groups of different study progression, there was a statistically significant difference in the proportion of antitumor drugs (P value = 0.0001) as well as those that required CMA, PASS, or PAES (P value = 0.0230).

Table 4. Overview of the study status of approvals

	Drug approved with ongoing study[b] (n = 17)	**Drug approved with completed study[c] (n = 24)**	**Total (n = 41)**	***P* value[d]**
Pivotal trial, n(%)				0.7113
Yes	14 (82.35)	18 (75.00)	32 (78.05)	
No	3 (17.65)	6 (25.00)	9 (21.95)	
Design types, n(%)				0.1932
Seamless design	6 (35.29)	9 (37.50)	15 (36.59)	
Group sequential	9 (52.94)	8 (33.33)	17 (41.46)	
Sample size re-estimation	1 (5.88)	0 (0.00)	1 (2.44)	
Combined group[a]	0 (0.00)	1 (4.17)	1 (2.44)	
Adaptations to treatment arm selection	0 (0.00)	1 (4.17)	1 (2.44)	
Adaptive dose-ranging	0 (0.00)	1 (4.17)	1 (2.44)	
Basket study	1 (5.88)	0 (0.00)	1 (2.44)	

Enrichment design	0 (0.00)	4 (16.67)	4 (9.76)	
Orphan drug, n(%)				0.1887
Yes	8 (47.06)	6 (25.00)	14 (34.15)	
No	9 (52.94)	18 (75.00)	27 (65.85)	
Antitumor drug, n(%)				**0.0001**
Yes	14 (82.35)	5 (20.83)	19 (46.34)	
No	3 (17.65)	19 (79.17)	22 (53.66)	
Accelerated assessment, n(%)				1.0000
Yes	1 (5.88)	2 (8.33)	3 (7.32)	
No	16 (94.12)	22 (91.67)	38 (92.68)	
New active substance, n(%)				0.2623
Yes	15 (88.24)	17 (70.83)	32 (78.05)	
No	2 (11.76)	7 (29.17)	9 (21.95)	
Additional monitoring, n(%)				0.1120
Yes	12 (70.59)	10 (41.67)	22 (53.66)	
No	5 (29.41)	14 (58.33)	19 (46.34)	
CMA, PASS, PAES n(%)[e]				**0.0230**
Yes	11 (64.71)	6 (25.00)	17 (41.46)	
No	6 (35.29)	18 (75.00)	24 (58.54)	
System organ class of indications, n(%)				0.1201
Nervous system disorders	0 (0.00)	1 (4.17)	1 (2.44)	
Congenital, familial, and genetic disorders	1 (5.88)	1 (4.17)	2 (4.88)	
Renal and urinary disorder	1 (5.88)	1 (4.17)	2 (4.88)	
Respiratory, thoracic, and mediastinal disorders	1 (5.88)	3 (12.50)	4 (9.76)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (35.29)	1 (4.17)	7 (18.92)	

Blood and lymphatic system disorders	5 (29.41)	3 (12.50)	8 (19.51)
Gastrointestinal disorders	1 (5.88)	3 (12.50)	4 (8.11)
Skin and subcutaneous tissue disorders	0 (0.00)	3 (12.50)	3 (7.32)
Immune system disorders	0 (0.00)	2 (8.33)	2 (4.88)
Vascular disorders	0 (0.00)	2 (8.33)	2 (4.88)
Metabolism and nutrition disorders	0 (0.00)	1 (4.17)	1 (2.44)
Cardiac disorders	0 (0.00)	1 (4.17)	1 (2.44)
Infections and infestations	2 (11.76)	0 (0.00)	2 (4.88)
Psychiatric disorders	0 (0.00)	1 (4.17)	1 (2.44)
Musculoskeletal and connective tissue disorders	0 (0.00)	1 (4.17)	1 (2.44)

a: Sample size re-estimation and enrichment design

b: Marketing authorization was granted to the drug for which clinical trials at the time were ongoing

c: Marketing authorization was granted to the drug for which clinical trials at the time were completed

d: Fisher's exact test was conducted

e: Conditional marketing authorisation, Post-authorisation safety study, Post-authorisation efficacy study

DISCUSSION

Instead of lightening the burden of rigorous clinical planning, using prespecified and planned adaptive designs in the development of medicinal products under experimental dilemmas is recommended. The flexibility and other advantages of adaptive designs over traditional clinical trial designs are being increasingly acknowledged after much effort was devoted to maintaining the type I error probability. Despite the warnings about potential biases and possible inflation of type I error probability, the EMA guidance on adaptive designs acknowledges the value of adaptive designs to innovate clinical trials in the development of new drugs and biologics.

After analyzing all available approval documentation, we observed that adaptive design trials could provide information on clinical efficacy that impacts regulatory decision-making. Furthermore, we found that sponsors and regulators increasingly included adaptive design trials in the approval package. Our study showed that the most popular adaptive designs were group sequential and seamless designs. Adaptive design can be pivotal in supporting the development of NASs. However, such trials face difficulties in supporting accelerated assessment, and AM requirements must be met.

The less common side effects of medicinal products are often difficult to identify in the short-term. Therefore, adverse drug reaction (ADR) reporting is an essential part of the surveillance after the introduction of new medicines to the market. However, underreporting is a recognized challenge and is reported to be as high as 94% [11, 12]. To increase ADR reporting, numerous bills were introduced [13-15]. One of these was AM. The designation of AM is aimed at encouraging the reporting of spontaneous side effects for new products

for which the safety profile may not be entirely established. The objective is to collect as much information as possible in order to interpret the risk profile and inform healthcare professionals and patients [14, 15]. The concept of AM was introduced by the 2010 pharmacovigilance legislation and became operative in 2012 [16]. The milestones for adaptive design and the AM list of EMA are presented in Figure 4.

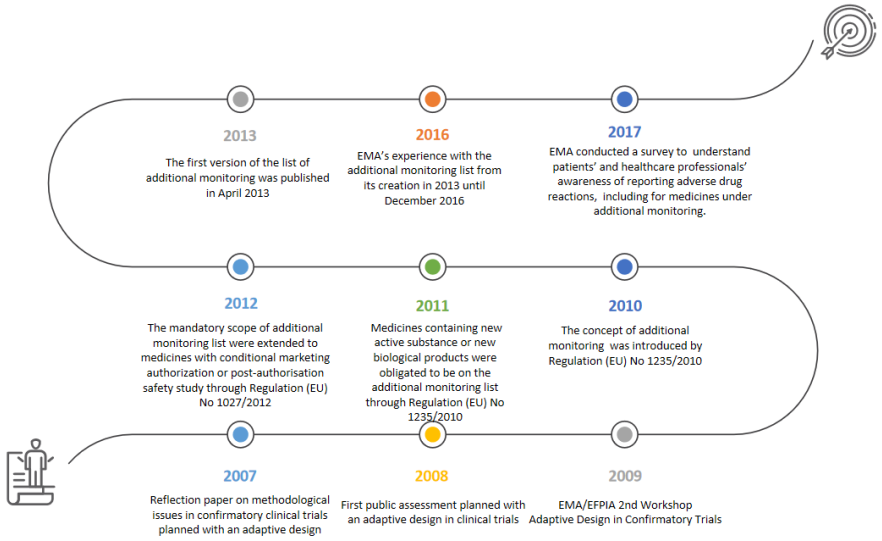

Figure 4. Milestones for adaptive design and additional monitoring list of EMA

In addition to the issue that adaptive designs might expand type I errors, there are other concerns, such as blinding and operational bias, interim analyses bias, and so on. We found that 90% of the approvals with adaptive designs in the past 5 years were required to undertake AM, which reflected the cautious attitude of the regulator even though AM was originally for ADR purposes. However, in 2017, the EMA conducted a public survey to assess the awareness of reporting ADRs, including for medicines under AM. This survey showed that the perceived level of AM varied in different groups. Among all respondents, fewer than half displayed a preferable understanding of the concept. In other words, fewer than half of respondents were aware of reporting ADR spontaneously. AM status played an indecisive role in the reporting of ADR. Therefore, it is easy to wonder how well AM protects against the risks from adaptive designs.

In general, cancer patients do not have time to wait for the results of randomized clinical trials, so they need access to drugs that demonstrate safety profiles in phase I/II studies [17]. Based on these justifications, antitumor drugs may be more likely to be granted marketing authorization before the completion of the whole clinical trial once the efficacy and safety profile have fulfilled the requirements of regulatory authorities. Therefore, group sequential design might be considered a preliminary approach in the long-term development of antitumor medicines, especially for rare diseases or public health emergencies. However, after examining 17 group sequential designs, our results showed that only 4 of them complied with rules for stopping early based on interim efficacy results. This suggests that the success rate for the other 13 drugs was not increased even though their trials used adaptive designs. Furthermore, as well as being stopped for efficacy, group sequential designs can also be halted based on futility to reduce the high cost of drug development. In our study, 41.46% of clinical studies containing adaptive designs continued after the drug was approved. Although study progression might not have an influence on the decision of granting marketing authorization to products, this result revealed the pervasiveness and power of these studies to build up an eligible efficacy and safety profile. Our review of the regulatory measures of EMA showed that products granted marketing authorization with ongoing trials were more likely to be required to submit safety or efficacy studies in postauthorization or to be granted CMAs, which are valid for 1 year and can be renewed annually.

Conclusion

Adaptive design is a double-edged sword. It is capable of expediting the process of medicine development by reducing the study duration and sample size. On the other hand, it may require more regulatory measures for drugs for which the safety profile has not been rigorously established. As a result, the importance of crisis awareness should be raised because the number of medicines falling under AM is growing, especially for those with adaptive scheduling in confirmatory trials. We are curious to know what role adaptive design has in ongoing studies when the drug is approved, the current regulations (AM, CMA, PASS) are helpful to build up completed safety profiles for these drug are expected to be explored and detailed in the future.

data availability statement

Research data are not shared.

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