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EDITORS' CHOICE

Flexible approaches to clinical trials

In the February 2023 issue of the *Journal of Clinical Epidemiology*, two papers focus on flexible approaches to clinical trials; one on adaptive trial designs [1] and the other on adaptive interventions examined in clinical trials [2]. According to the Federal Drug Administration (FDA), an adaptive trial is "a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial" [3]. In contrast, clinical trials examining adaptive interventions occur when data continuously collected from patients are used to tailor their management on an ongoing basis [2]. Adaptive trial designs use a flexible approach to the entire trial process, whereas adaptive interventions use a flexible approach to the intervention only. In a sense, both adaptive trials and adaptive interventions are more reflective of the real world where a patient's management plan is tailored according to their response throughout the trial.

Specific to adaptive trials, there are many important benefits compared to the traditional fixed-design trial [3]. Adaptive trials provide greater statistical efficiency [3]. For example, the same degree of statistical power can be achieved with smaller sample sizes because ineffective treatments or doses can be abandoned and more patients will be switched to treatments shown to be effective [4]. Adaptive trials might be considered more ethical in some cases because a trial can be stopped earlier if the intervention is shown to cause harm or not be effective, with the opportunity to continue participation and explore different interventions [3]. Due to the flexible nature, an adaptive trial can be used to answer broader questions compared with a traditional fixed-design trial, thereby providing more information regarding an intervention's effect [3]. An adaptive trial, in some cases, might be more acceptable than traditional fixed-design trials to end users, such as patients and trial funders. This is because the trial conduct is modified using a plan established a priori according to the patient's response to important outcomes [3].

By its nature, an adaptive trial is more complex than a traditional fixed-design trial. As such, there is a greater chance that trials with adaptive designs can be biased [3]. Several additional methodological nuances need to be addressed in the conduct of an adaptive trial, and more extensive planning is required. For example, ensuring modifications are established a priori for patients according to specific outcomes or results that are measured at predefined intervals [3]. Ensuring that the trial conduct and integrity are maintained throughout the trial is another important consideration [3]. For example, outcome assessors should be independent from the individuals collecting the patient data to ensure that decisions such as stopping the trial early for lack of effect are unbiased by personal interactions with the patient [3]. Because adaptive trials are more complex than a traditional fixed-design trial, advanced statistical methods are required [3]. This is to ensure that erroneous results and conclusions are minimized and avoided as much as possible. More information on the conduct of adaptive trials can be found in the FDA guide [3].

It is clear that adaptive trials require more planning and methodological considerations for their conduct than a traditional fixed-design trial. As such, it makes sense that more information will be required when reporting trials with adaptive designs. The Consolidated Standards Of Reporting Trials (CONSORT) statement was published in 2010 to improve the reporting of clinical trials [5]. A systematic review published in Cochrane in 2012 included 50 evaluations after searching several databases from inception until 2010 [6]. The authors concluded that trials published in journals that endorsed the CONSORT statement had a greater quality of reporting than those published in journals that did not endorse CONSORT [6]. This provides evidence that the use of the CONSORT reporting guidance can potentially improve the reporting of clinical trials.

Many elements of the CONSORT statement can be used to assess the reporting of trials with adaptive designs [5]. However, just as there are methodological nuances to adaptive trials, there are differences in reporting standards. To address this, the Adaptive Designs CONSORT Extension (ACE) statement was published in 2020 for the reporting of trials with adaptive designs [7]. The ACE checklist includes several additional items and also modification of others in the CONSORT statement [7]. These covered multiple issues, including preplanning adaptive design features, evaluation of interim results, adaptation decisions, confidentiality of results, sample size calculations, and stopping rules, among others [7].

In this issue of the *Journal of Clinical Epidemiology*, Purja and colleagues (2023) explored the quality of reporting for trials with adaptive designs [1]. A sample of 109 clinical trials with adaptive designs was obtained after searching multiple databases (e.g., PubMed, Embase, Cochrane Library, Web of Science, Google Scholar) from inception until November 2022 [1]. The included studies were assessed using the ACE checklist [7] for completeness of reporting [1].

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The authors found that the overall reporting score was 69.8% across the trials, ranging from 21.1% to 97.4% [1]. Twelve factors were analyzed to determine their association with the overall reporting score [1]. Study-level factors potentially associated with better study reporting included a registered trial, publication in a general medical journal, publication after the year 2020, and including more than 100 patients [1]. Author-related factors potentially associated with better reporting included the authors reporting the number of interim analyses planned, the first author being not affiliated with industry, and the adaptive trial being free from industry funding [1]. The authors conclude that there is room for improvement in the reporting of trials with adaptive designs [1]. Future studies in this area could examine the endorsement by journals of the ACE checklist [7] and whether this improves the quality of reporting over time.

A second paper in this issue of the *Journal of Clinical Epidemiology* focused on adaptive interventions used in trials, specifically on "just-in-time adaptive interventions" [2]. A just-in-time adaptive intervention occurs when data are continuously collected from patients and their treatment management is almost instantaneously tailored, often using artificial intelligence [2]. An example of this type of interventions is when a patient uses a continuous-glucose-monitoring device and the data are sent to a computer database that is automated to provide real-time adjustment of insulin through the patient's insulin pump [8]. The use of adaptive interventions allows for many of the same benefits as trials with adaptive designs that were outlined above—a patient's intervention can be tailored according to their response to the intervention, it is more consistent with the real world, and potentially more acceptable to end users of trials. Similar to trials that use adaptive designs, methodological nuances and subsequent reporting elements are unique to trials that examine adaptive interventions as well.

Oikonomidi and colleagues (2023) conducted a scoping review of just-in-time adaptive interventions [2]. Eighty-eight trials were included after searching multiple databases (e.g., PubMed, PsycINFO, Web of Science) from January 2019 until March 2021 [2]. The authors assessed the included articles for reporting completeness using customized components that were based on pre-existing reporting guidance [2]. Similar to the 2023 article by Purja and colleagues [1], they used the CONSORT 2020 statement [5] for clinical trials. They also used a reporting guide that was developed for the details of interventions used in trials: the template for intervention description and replication (or TIDieR) checklist [9]. The specific reporting elements they focused on were details related to the (1) level of tailoring used to select the intervention, (2) decision points when the patient may require support to properly use the intervention, (3) decision rules for tailoring the intervention according to the patient's response, and (4) different intervention component options that could be offered to the patient [2]. The authors found that only 23% of the included trials reported on all four components [2]. Because the focus was on "just-in-time" interventions, they also examined the degree to which the intervention was delivered using artificial intelligence with five levels of automation: no automation, assistance, partial automation, high automation, and full automation [2]. More than half of the trials used interventions that were either fully automated or highly automated [2]. The authors concluded that there is room for improvement in the reporting of trials examining just-in-time adaptive interventions [2]. Future research in this area could include a sample with a longer time frame to examine trends in the quality of reporting over time.

The two articles highlighted from this issue of the *Journal of Clinical Epidemiology* cover flexible clinical trial designs, whether for the entire trial, as in an adaptive trial [1], or for tailoring the intervention, as in the just-in-time adaptive intervention [2]. In both cases, we see that there are several benefits to these flexible designs, which need to be balanced carefully against their potential methodological challenges and increased reporting element requirements. In both these articles, the authors concluded that the quality of reporting was suboptimal and could be improved. It is hoped that by raising awareness of the issues, these flexible clinical trial designs will be better reported in the future.

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