Title

stata.com

Intro — Introduction to adaptive designs for clinical trials

Description

This entry provides a brief introduction to adaptive designs for clinical trials. For a general introduction to group sequential designs and their implementation in Stata, see [ADAPT] **GSD intro** and [ADAPT] **gs**, respectively.

Remarks and examples

stata.com

Armitage (1993) observes that "classical theory of experimental design deals predominantly with experiments of predetermined size, presumably because the pioneers of the subject, particularly R. A. Fisher, worked in agricultural research, where the outcome of a field trial is not available until long after the experiment has been designed and started." This type of study, where the target sample size is fixed during the design stage, is known as a fixed-sample design (FSD). In other applications, it is common for data to trickle in, providing researchers the opportunity to conduct interim analyses of a partial dataset. This is especially common in clinical trials—studies examining the effects of treatments on humans—where participants are usually accrued over time.

An alternative to an FSD is an adaptive design, a type of experimental design increasingly popular for clinical trials. The U.S. Food and Drug Administration (2019) describes an adaptive design as "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." By providing a framework to modify aspects of the study design, an adaptive design allows the trial to be adjusted to account for information that was unavailable during the design stage.

Adaptive designs for clinical trials offer several potential advantages over FSDs. Many adaptive designs offer the prospect of increased statistical efficiency, often in the form of a smaller expected sample size than that of an equivalently powered FSD. This can save resources for the sponsor of the trial. Resources can also be saved by employing adaptations that modify the recruitment practices or the desired sample size of an ongoing trial to maximize the probability of identifying a clinically meaningful treatment effect. There is also an ethical argument for some adaptations, particularly those that reduce the number of participants assigned to ineffective treatments. Some adaptations even allow the trial to test additional hypotheses that were not considered during the design stage, such as whether a treatment is particularly effective in some subgroups of the population.

Adaptive designs are not a panacea for all challenges encountered during a clinical trial, and this has led some authors to caution against viewing adaptive designs as a distinct class of clinical trials. Piantadosi (2017, 416), for example, advocates using the term "adaptive design features" to emphasize that adaptations are tools for a trialist, not an alternative to addressing underlying issues in a clinical trial design.

Adaptive designs are not without their drawbacks, often in the form of increased complexity. Sample-size calculations and statistical analysis of adaptive designs are typically more complicated than the equivalent methods for FSDs. The implementation of an adaptive design adds logistical challenges: interim analyses require timely and accurate data to be reported multiple times over the course of the trial, and adaptations to the way participants are assigned to treatment groups add

complexity to the recruitment process. Also, even if an adaptive design has a smaller expected sample size than a similarly powered FSD, the adaptive design may have a larger maximum sample size. This is because the expected sample size is the average sample size if the trial were to be repeated many times, while the maximum sample size is the largest possible sample under the adaptive design.

The most popular forms of adaptive designs for clinical trials fall into several broad categories.

- **Group sequential designs** provide the ability to stop a trial early if an interim analysis of the data provides compelling evidence that a treatment is effective or ineffective. This is one of the most widely used adaptive designs and will be the focus of this manual.
- **Adaptive methods for sample-size modification** allow the desired sample size to be adjusted while the trial is underway. Blinded sample-size reestimation adjusts the sample size based on estimates of nuisance parameters (such as the variance of a normal mean) that have been pooled over all treatment groups, while unblinded sample-size reestimation can use estimates of nuisance parameters from individual treatment groups or even interim estimates of the treatment effect.
- **Adaptive randomization designs** modify the way participants are randomized (allocated) to treatment groups. Covariate-adaptive randomization seeks to reduce differences in the distribution of covariates in the treatment groups by modifying the probability that a participant will be assigned to a treatment group based on covariate data collected from the participant before randomization. Response-adaptive randomization modifies allocation probabilities based on interim estimates of treatment effects and can be used to reduce the number of participants assigned to less effective treatments.
- **Adaptive designs for treatment-arm modification** allow the addition or removal of treatment groups, or arms, during the course of the study. Examples include early-phase dose-finding trials that add or remove arms at different dosage levels, and late-phase multiarm trials that "drop the loser", terminating one arm at a time. Large-scale ongoing adaptive platform trials follow a prespecified master protocol to compare multiple experimental arms against a single treatment arm; new experimental arms are added as new treatments become available, and experimental arms may be terminated based on the results of interim analyses.
- **Adaptive enrichment designs** typically begin by enrolling participants from a diverse population and use interim data about treatment efficacy to restrict subsequent recruitment to targeted population subgroups. This approach is particularly appealing when participant characteristics, such as genetic markers, are believed to play a role in treatment efficacy.

Adaptive design of clinical trials is a topic of active research, and the list above is by no means exhaustive. In what follows, we focus on group sequential designs. For more information about adaptive designs, see Pong and Chow (2010), Chow and Chang (2012), Bhatt and Mehta (2016), Pallmann et al. (2018), and U.S. Food and Drug Administration (2019).

References

Armitage, P. 1993. Interim analyses in clinical trials. In *Multiple Comparisons, Selection, and Applications in Biometry*, ed. F. M. Hoppe, 391–402. Boca Raton, FL: CRC Press.

Bhatt, D. L., and C. R. Mehta. 2016. Adaptive designs for clinical trials. *New England Journal of Medicine* 375: 65–74. https://doi.org/10.1056/NEJMra1510061.

Choodari-Oskooei, B., D. J. Bratton, and M. K. B. Parmar. 2023. Facilities for optimizing and designing multiarm multistage (MAMS) randomized controlled trials with binary outcomes. *Stata Journal* 23: 774–798.

Chow, S.-C., and M. Chang. 2012. *Adaptive Design Methods in Clinical Trials*. 2nd ed. Boca Raton, FL: CRC Press.

Pallmann, P., A. W. Bedding, B. Choodari-Oskooei, M. Dimairo, L. Flight, L. V. Hampson, J. Holmes, A. P. Mander, L. Odondi, M. R. Sydes, S. S. Villar, J. M. S. Wason, C. J. Weir, G. M. Wheeler, C. Yap, and T. Jaki. 2018.

Adaptive designs in clinical trials: Why use them, and how to run and report them. *BMC Medicine* 16: 29. https://doi.org/10.1186/s12916-018-1017-7.

Piantadosi, S. 2017. *Clinical Trials: A Methodologic Perspective*. 3rd ed. Hoboken, NJ: Wiley.

Pong, A., and S.-C. Chow, ed. 2010. *Handbook of Adaptive Designs in Pharmaceutical and Clinical Development*. Boca Raton, FL: CRC Press. https://doi.org/10.1201/b10279.

U.S. Food and Drug Administration. 2019. *Adaptive Designs for Clinical Trials of Drugs and Biologics: Guidance for Industry*. Docket No. FDA-2018-D-3124. Silver Spring, MD. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry.

Also see

[ADAPT] **GSD intro** — Introduction to group sequential designs

[ADAPT] **gs** — Introduction to commands for group sequential design

[ADAPT] **Glossary**