Summary
Adaptive and Novel Trial Designs

The CADTH Guidelines for the Economic Evaluation of Health Technologies: Canada details best practices for conducting economic evaluations in Canada. In 2014, CADTH began the process of updating this document and identified a number of technical areas where additional information would assist in the update. CADTH then commissioned work from experts in the field to produce a series of technical reports. This brief summarizes one of these reports.

The report Adaptive and Novel Trial Designs describes the major types of adaptive trials, highlights key novel trial designs, and discusses the potential limitations of each design from a clinical methodological perspective. To supplement the discussion of the limitations and critical appraisal points, related guidance from regulatory bodies and the viewpoint of the Pharmaceutical Research and Manufacturers of America will also be presented, where available. In addition, the implications that particular features of adaptive or novel trial designs may have when considering the interpretation or potential generalizability of the results are discussed. The report focuses on the adaptive and novel designs used in confirmatory phase studies.

What are adaptive and novel trial designs?

While there is no single definition, the European Medicines Agency (EMA) defines an adaptive trial as one in which "statistical methodology allows modification of a design element (for example, sample size, randomization ratio, number of treatment arms) and an interim analysis with full control of the type I error." Using an adaptive trial design may be appealing for a number of reasons. Depending on the specific approach used, an adaptation may improve a trial's efficiency by reducing the sample size requirement or by shortening the trial duration, make the trial more informative by providing more detailed information on the relationship between dose and response, or improve a trial's ability to demonstrate a treatment effect. There are also some novel, non-adaptive trial design features that can be incorporated into a clinical trial. For example enrichment strategies can be used to select a subset of the population in which a treatment effect may be more readily demonstrated.

In spite of the potential benefits, there are also some limitations with the use of adaptive and novel trial designs. For example, there is potential for an adaptive design feature to bias estimates of treatment effect and increase the risk of misleading findings. And, in the case of an enrichment strategy, limiting the inclusion population to a specific subgroup can potentially impact the generalizability of estimated treatment effects.

Which adaptive and novel trial designs does this report cover?

The report outlines the potential advantages and limitations of the following adaptive and novel trial designs:

- Combined Phase II/III design
- Adaptive randomization designs — including covariate-adaptive, treatment-adaptive, and response-adaptive designs Sample size re-estimation
- Stepped wedge randomization design
- Enrichment designs — including strategies to decrease heterogeneity, prognostic enrichment strategies, and predictive enrichment strategies.

For more information, please visit:
cadth.ca/economic-evaluation-guidelines-update

ABOUT CADTH
CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs and medical devices in our health care system.
CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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