

**Final Concept Paper
E20: Adaptive Clinical Trials
Dated 7 November 2019**

Endorsed by the Management Committee on 18 November 2019

Type of Harmonisation Action Proposed

A new guideline on the design, conduct, analysis, and interpretation of adaptive clinical trials that provides a transparent and harmonized set of principles for the regulatory review of these studies in a global drug development program. These principles should also provide the flexibility to evaluate / discuss innovative approaches to clinical trial design throughout the development process. For the purposes of this document, adaptive clinical trials are defined as trials planned with an adaptive design.

Statement of the Perceived Problem

Although the European and US regulatory agencies have issued a reflection paper and draft guidance for adaptive clinical trials, respectively, these advisory documents themselves are not fully harmonized. Further adoption of such innovative clinical trials will be limited without a harmonized perspective from drug regulatory agencies, especially for confirmatory studies in global drug development programs. Different perspectives among regulatory agencies in different regions have resulted in uncertainty in the use of adaptive clinical trials in a global environment.

In particular, definitions related to adaptive clinical trials are sometimes inconsistent. There are no common principles for the design, conduct, analysis, and interpretation of adaptive clinical trials, especially in relationship to the risk of erroneous conclusions and maintenance of trial integrity. There are also no common expectations for documentation to support regulatory review of adaptive clinical trials. These issues hinder further adoption of adaptive designs across drug development. Without a harmonized perspective for adaptive clinical trials among the different ICH regions, sponsors and regulators are limited in their ability to build an efficient multi-regional prospective plan for drug development which incorporates these innovative designs.

Issues to be Resolved

This global harmonized regulatory guideline will address:

- A common terminology for adaptive clinical trials
- The potential benefits of adaptive clinical trials and areas (e.g., study settings and design features) of meaningful applications
- The principles for the design, conduct, analysis, and proper interpretation of adaptive clinical trials, including considerations of the risk of erroneous conclusions (e.g., control of false positive and false negative conclusions, and reliability of effect estimates), maintenance of trial integrity, and handling of operational challenges
- The documentation that is important for the planning and implementation of adaptive clinical trials and the interactions between sponsors and regulatory agencies.

While adaptive clinical trials throughout all stages of development are in scope, the primary focus of the guideline will be on confirmatory clinical trials.

Background to the Proposal

There is an increasing interest in using adaptive clinical trials in modern drug development. Potential advantages of adaptive designs include limiting patient exposure to unsafe or ineffective treatments, savings of trial resources, and accelerating the development process while ensuring that the adaptive clinical trials can provide the evidence for regulatory decision making. However, there are uncertainties due to the lack of common principles for the design, conduct, analysis, and interpretation of adaptive clinical trials and the lack of common expectations for documentation to support regulatory review. Hence, it is critical to develop a harmonized guideline to eliminate some of the limiting factors and ensure appropriate use of the potentially efficient designs in global development of effective treatments.

Type of Expert Working Group and Resources

The Expert Working Group (EWG) should consist of ICH Members and Observers in accordance with the applicable rules of procedure and standard operating procedures. The expertise should be a balance of clinical and statistical experts with experience in innovative clinical trial approaches.

Timing

An Informal Work Group was launched in June 2019 to finalize the Concept Paper prior to the formation of an ICH EWG. The work of the EWG will take approximately 3 – 4 years to complete.