Final Business Plan
E20: Adaptive Clinical Trials
Dated 7 November 2019
Endorsed by the Management Committee on 18 November 2019

1. The issue and its costs

- *What problem/issue is the proposal expected to tackle?*

  The European and US regulatory agencies have issued a reflection paper and draft guidances for adaptive clinical trials[1], respectively. However, in these advisory documents and even in the public literature, there are some differences with regards to, among others:
  - The terminology for adaptive clinical trials,
  - The principles for the design, conduct, analysis, and proper interpretation of adaptive clinical trials, and
  - The documentation that is important for the planning and implementation of adaptive clinical trials and the interactions between sponsors and regulatory agencies.

  The lack of harmonized guideline on adaptive clinical trials hinders the use of these innovative designs in global drug development programs in instances where they may be able to provide added value to drug development while maintiaining the evidence for regulatory decision making.

- *What are the costs (social/health and financial) to our stakeholders associated with the current situation or associated with "non action"?*

  The lack of harmonization related to adaptive clinical trials has created uncertainty and limited the ability of sponsors and regulators to build an efficient multi-regional prospective plan for global clinical development programs which incorporates these innovative designs. This can potentially result in delay in clinical development process, increase in development cost when different regulatory agencies have different requests, overexposure of inefficacious experimental treatments to patients, and different/inconsistent approval decisions among regulators.

2. Planning

- *What are the main deliverables?*

  The main deliverable is a harmonized guideline on adaptive clinical trials, which will provide clarity on
  - 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

[1] For the purposes of this document, adaptive clinical trials are defined as trials planned with an adaptive design.

- 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.

Training materials will be developed to facilitate the implementation of the E20 guideline. Additional deliverables may include, for example, surveys of stakeholders, education, and a regional public workshop(s) to ensure appropriate use of adaptive clinical trials.

- *What resources (financial and human) would be required?*

  Formation of an Expert Working Group (EWG), which should consist of ICH Members and Observers in accordance with the applicable standard operating procedures. The EWG should be made up of clinical and statistical experts with experience in innovative clinical trials.

- *What is the time frame of the project?*

  The work of the EWG will take approximately 3 - 4 years to complete.

  The EWG plans to develop training materials while working on the E20 guideline document. In addition, we plan to engage stakeholders and if needed, conduct a survey(s) of stakeholders and hold regional workshop(s) during the consultation period to ensure sufficient training is available and that the guidelines are being implemented appropriately. To accomplish these goals, the work of the EWG will take approximately 3 - 4 years to complete.

- *What will be the key milestones?*

  The final concept paper will be submitted to the Management Committee (MC) in September 2019 with an expectation of an EWG face-to-face meeting in November 2019. Step 2 a/b document is planned to be completed by June - November 2021 and Step 4 is anticipated to be reached by November 2022 or 2023.

- *What special actions to advance the topic through ICH, e.g. stakeholder engagement or training, can be anticipated either in the development of the guideline or for its implementation?*

  Consultation with additional experts may be required to develop the guideline and provide training. Surveys of stakeholders may also be conducted to ensure sufficient training is available and that the guidelines are being implemented appropriately.

3. The impacts of the project

- *What are the likely benefits (social, health and financial) to our key stakeholders of the fulfilment of the objective?*

  It will eliminate some of the limiting factors and ensure appropriate use of the potentially more efficient designs in global development of effective treatments. This can potentially result in limiting patient exposure to unsafe or ineffective treatments, savings of trial resources, and accelerating the development process while maintaining evidentiary standards.

- *What are the regulatory implications of the proposed work – is the topic feasible (implementable) from a regulatory standpoint?*

  The proposal is consistent with current laws and regulations of the ICH regions. Regulatory authorities responsible for reviewing clinical development applications will need to agree globally on the principles for the design, conduct, analysis and proper interpretation of adaptive clinical trials as well as the recommendations for the documentation that are important for the planning and implementation of adaptive clinical trials and the interactions between sponsors and regulatory agencies. This guideline will supersede and update regional guidelines, enabling the appropriate use of adaptive designs in global clinical development based on the harmonised guideline.

- *Will the guideline have implications for the submission of content in the CTD/eCTD? If so, how will the working group address submission of content in the dossier? Will a consult be requested with the ICH M8 working group?*

  No, the E20 guideline will not have implications for the submission of content in the CTD/eCTD, which shall follow the ICH M8 guideline. The E20 guideline is expected to be aligned with other previous ICH guidelines.

4. Post-hoc evaluation

- *How and when will the results of the work be evaluated?*
  The results will be evaluated by:
  - Implementation of local regulations and/or guidance documents that align with the final guideline;
  - Surveys of stakeholders may also be conducted to ensure sufficient training is available and that the guidelines are being implemented appropriately.