Final Business Plan
ICH E6(R3): Guideline for Good Clinical Practice
Dated 17 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?*

  In the two decades since ICH E6 was first drafted, clinical trials have become more complex with respect to trial design, use of technology, quantity of data collected and involvement of central testing facilities or other service providers. ICH E6(R2) was developed with multiple addenda to address the emerging use of electronic data sources and risk management processes. However, since the development of E6(R2), clinical trials have continued to evolve with new designs and technological innovations. There is also a desire that E6(R3) should be developed to provide guidance that is applicable to different clinical trial designs and to focus on key principles and objectives. E6(R2) included a focus on a proportionate, risk-based approach to the design and conduct of clinical trials. E6(R3) will be designed to further advance this concept and to encourage relevant parties to utilize this approach.

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

  E6(R2) is not fully designed to address emerging technologies, innovations in trial design, the diversity of data sources, testing facilities, and service providers, or to address other emerging complexities of the current clinical trial climate. In the absence of a modernized guideline, reference may be made to the current provisions in E6, even though the requirements may not be fully adapted to these technologies, or stakeholders may fail to adopt the current requirements. The application of the current standard to new technology is clearly challenging. Consequently, the design and conduct of trials, including in particular investigator site, test facility or service provider activities and record-keeping, may fail to take full advantage of technological innovations and the full potential of the risk-based considerations related to participant protection, data integrity or other public health considerations.

2. Planning

- *What are the main deliverables?*

  This work will set out principles which will be aligned with those set out in E8(R1) *Revision of General Considerations for Clinical Studies*. When complete, E6(R3) will be composed of an overarching principles and objectives document, Annex 1 (interventional clinical trials), and Annex 2 (additional considerations for non-traditional interventional clinical trials). The overaching principles and objectives document and Annex 1 will replace the current E6(R2).

The development of Annex 2 will commence once the principles and objectives document and Annex 1 complete ICH *Step 1*. The revision aims to address identified gaps or inconsistencies in existing ICH guidances as appropriate.

The proposed rewrite will include more specific discussions and refinement to E6 principles in the context of different trial types and data sources in the annexes as described below:

- Annex 1 - Interventional clinical trials

  This will include the use of unapproved or approved drugs in a controlled setting with prospective allocation of treatment to participants and collection of trial data. This Annex will be developed simultaneously with the principles and objectives document to ensure consistency and to provide stakeholders with a complete package that can replace E6(R2); and

- Annex 2 - Additional considerations for non-traditional interventional clinical trials

  This will include designs such as pragmatic clinical trials and decentralized clinical trials, as well as those trials that incorporate real world data sources. Before the drafting of Annex 2, its scope will be further clarified, to define the nature of trials involved, in an update to this concept paper.

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

  The EWG will include experts from various disciplines including clinical, statistical, data science, clinical outcomes assessment, regulatory compliance, and potentially others. The group should have overlap of expertise with the experts of the E8 EWG and work in close collaboration with them. The work of the group will involve engagements with a variety of stakeholders including academia and patient advocacy groups throughout the development process.

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

  Fall 2019 through Fall of 2021.

  This work is considered time-critical and highly anticipated by the regulated community. The working group was launched in September of 2019 and the first face-to-face meeting is scheduled for November of 2019. It is anticipated that the process to create the overarching principles and objectives document and Annex 1 is expected to take 18 - 24 months to reach *Step 1*, once the concept paper and business plan are endorsed. After the priniciples and objectives document and Annex 1 complete *Step 1*, the work on Annex 2 will commence.

- *What will be the key milestones?*

  The established ICH processes and procedures should be followed. The proposed revision is expected to take approximately 18-24 months to reach Step 1.

- *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?*

  The EWG will plan and execute multiple engagements with other ICH groups (especially the group working on E8) to ensure mutual learning and consistency. The EWG is planning to engage with appropriate stakeholders, including those from academic and patient-advocacy backgrounds, to maximize the relevance and utility of E6(R3).

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?*

  The proposed revision to ICH E6 would likely primarily benefit innovators who typically conduct clinical trials, such as those in the pharmaceutical and biotech sectors. work will also inform innovators who are utilizing or exploring the use of diverse trial types and the data sources being employed to support regulatory and healthcare related decision-making on drugs, The revised E6 will highlight that achieving GCP principles and objectives can be accomplished through the use of multiple tools and methods. It will also highlight that the implementation of GCP principles should be a thoughtful, deliberative, and risk-based process as clinical trials can vary greatly and certain aspects of GCP may not be applicable to every trial. The revised E6 will take into consideration the diversity of clinical trials.

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

  We expect the revised E6 to be implementable from a regulatory perspective.

4. Post-hoc evaluation

- *How and when will the results of the work be evaluated?*
  The draft revisions will be subject to review and feedback from stakeholders. The development of annexes in addition to the principles document as a part of E6(R3) is expected to add robustness and flexibility that enables future adoption whenever appropriate.