ICH E20 – an industry perspective

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E20 Expert Working Group

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How it came about

- Established in 1990, the International Council of Harmonization (ICH) aims to harmonize the regulatory requirements for pharmaceutical products around the globe
  - Initially constituted by members from Europe, Japan, and the US
- ICH E20 Concept Paper released in November 2019
  - National guidelines for adaptive clinical trials issued by regulatory agencies (e.g., EMA, FDA, NMPA) not fully harmonized
- ICH E20 Expert Working Group (EWG) established to develop a harmonized guideline on 'Adaptive designs for clinical trials'
  - Dedicated section on the use of Bayesian methods in adaptive designs

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Definition of an Adaptive Design

"*For the purpose of this guideline, an adaptive design is defined as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the trial based on interim analysis of accumulating data from participants in the trial.*"

Scope

Focus is on confirmatory trials with an adaptive design

Out of scope:

- Trials with unplanned modifications to the design
- Design changes based entirely on emerging information from a source external to the trial
- Routine monitoring of operational aspects

Advantages and Challenges

- Adaptive designs come with advantages that are important and appreciated, but also with more uncertainty compared to non-adaptive designs
- "*In planning an adaptive design, it is therefore essential to carefully justify the need to adapt the trial and assess potential implications of the type, number, and complexity of the adaptations involved. […] It should weigh the advantages of the design against the extent to which the adaptations being considered add uncertainty about the trial's ability to produce reliable and interpretable results*."

Key Principles

- Adequacy within the development program
- Adequacy of trial planning
- Limiting the chances of erroneous conclusions
- Reliability of estimation
- Maintenance of trial integrity

"*All of these principles should be followed regardless of the type of adaptation and statistical approach (e.g., frequentist or Bayesian methods).*"

Key Principles

Limiting the chances of erroneous conclusions

- "*The common approach is to limit the probability of false positive efficacy conclusions within a trial by using frequentist methods that control the Type I error probability (ICH E9).*"
  - "*For most adaptive designs, it is necessary to use specific methods to control the Type I error probability.*"
- In adaptive designs using Bayesian methods, "*important considerations for limiting the chances of false positive efficacy conclusions*" apply

Key Principles

Reliability of estimation

- "... *provide an estimate of the treatment effect that is reliable and aligned with the estimand of interest*."
- "*Sponsors should evaluate bias and variability of treatment effect estimates, including measures such as the mean squared error. In the trade-off between bias and variance, the expectation is generally for limited to no bias in the primary estimate of the treatment effect.*"
- "*The primary analysis should also support calculation of accurate measures of uncertainty such as confidence intervals with targeted coverage probabilities.*"

Key Principles

Other Principles

Adequacy within the development program

- An adaptive clinical trial should be meaningful "*within the context of the overall development program*" and is not meant to be a "*replacement for a sequence of multiple trials*"
- "*Number and complexity of adaptations … should generally be limited.*"

Adequacy of trial planning

- "*… ensure the design is pre-specified, conduct and analysis are appropriate, and results are reliable and interpretable.*"
- "*There should be a justification for adapting aspects of the trial*"

Maintenance of trial integrity

- "*… blind participants, investigators, and sponsor to individual treatment assignments and to accumulating summary-level data in which treatment groups are identified …*"

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Adaptive Designs Using Bayesian Methods

Footnote to Section 5.3

"*This section on Bayesian methods for adaptive designs is not fully harmonized. The broad use of Bayesian methods may not be justified in all situations for regulatory decision-making. As noted in ICH E9 and in this draft guideline, the use of Bayesian methods in clinical trials may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust. Public consultation comments are sought on the topic, and on situations in which Bayesian methods satisfy the core adaptive design principles, and in which the use of Bayesian methods could be considered.*"

Adaptive Designs Using Bayesian Methods

General remarks

- "*ICH E9 notes that the use of Bayesian methods in clinical trials may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust.*"
- "*The principles outlined in Section 3 should be followed ...*"
- "*There are different types of application of Bayesian methods to clinical trials with an adaptive design, each with different considerations.*"

Adaptive Designs Using Bayesian Methods

One type of application

- Bayesian methods are used to "*inform adaptations in a trial where decision criteria for the primary analysis are chosen to ensure that the Type I error probability is controlled*."
- "*For example, a trial including interim analyses with pre-specified non-binding futility stopping rules … where the primary efficacy analysis [uses] a frequentist hypothesis test at a pre-specified significance level*"
  - Futility stopping rules can be based on posterior probabilities of an inefficacious treatment or predictive probabilities of rejecting the null hypothesis at trial end
- "*For such designs, expectations for operating characteristics are the same as for adaptive designs that do not involve Bayesian methods.*"
  - "*Sponsors should justify … prior distribution, decision criteria, and adaptive design elements … while maintaining Type I error probability control.*"

Adaptive Designs Using Bayesian Methods

Another type of application

- Bayesian methods are used to "*borrow external information based on an informative prior distribution, with decision criteria for the primary analysis based on the posterior distribution for the estimand of interest…*"
- "*Ensuring that a prior accurately reflects relevant available information and addressing the potential for conflict between prior and current trial data introduce additional uncertainties that are not present when using frequentist inference with no borrowing.*"
  - "*Misspecification of the prior distribution can lead to lack of control of the probability of false positive conclusions.*"
- Such designs "*require a thorough scientific justification that addresses the feasibility of alternative approaches not involving borrowing … and supports the relevance and quality of the external data.*"

Adaptive Designs Using Bayesian Methods

Another type of application (cont'd)

- When documenting the prior distribution in the protocol, discuss:
  - the source of the external information used to generate the prior
  - the relevance of the external information to the trial design
  - the list of all potentially relevant sources of information
  - why selected information sources were used and other potentially relevant sources were discarded
- "*Input from clinical subject matter experts is crucial …*"
- "*… data from randomized controlled trials and recent data are generally preferred*."
- "*Patient-level data are generally expected …*"

Adaptive Designs Using Bayesian Methods

Another type of application (cont'd)

- Evaluate to which extent such designs "*fulfill the principles … including control of the chances of false positive conclusions*."
  - "*Simulations should be performed … under various scenarios of prior-data conflict.*"
- "*Pre-specify and justify the details of a proposed prior distribution, including the amount of borrowing and criteria for defining trial success*."
  - "*… sufficient amount of current trial data to support benefit-risk assessment.*"
  - Discuss "*… strategies to mitigate the risk that observed trial data may conflict with the prior*" and "*including circumstances that would question the relevance of the external data and lead to no borrowing*."
- Include "*sensitivity analyses … to investigate the robustness of the trial conclusions against alternative reasonable choices for the prior distribution*."
  - "It is also important to evaluate the current trial data with no borrowing."

Conclusions

- ICH E20 supports the appropriate use of adaptive designs in confirmatory trials, with or without the use of Bayesian methods
- Adaptive designs present challenges compared to non-adaptive designs, as they may add complexities and uncertainty related to the key principles introduced in ICH E20
- Adaptive designs using Bayesian methods require additional justification as they may present additional uncertainty compared to a non-Bayesian design
  - Careful planning of prior distributions, decision criteria, and operating characteristics is needed to fulfill the principles from ICH E20
- While Bayesian methods may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust (ICH E9), the extent of their use remains unclear
  - Public consultation comments are sought on where Bayesian methods satisfy the core adaptive design principles and may be appropriate

Thank you