ICH E20 EWG on Adaptive Clinical Trials

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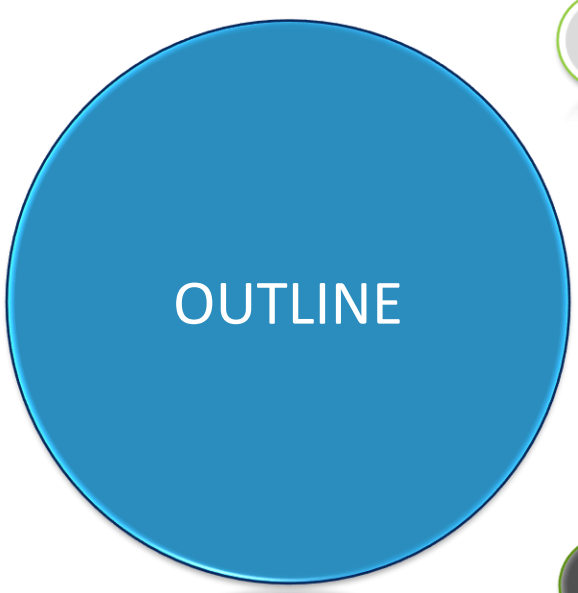
Janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson



1 **Background to the Proposal**

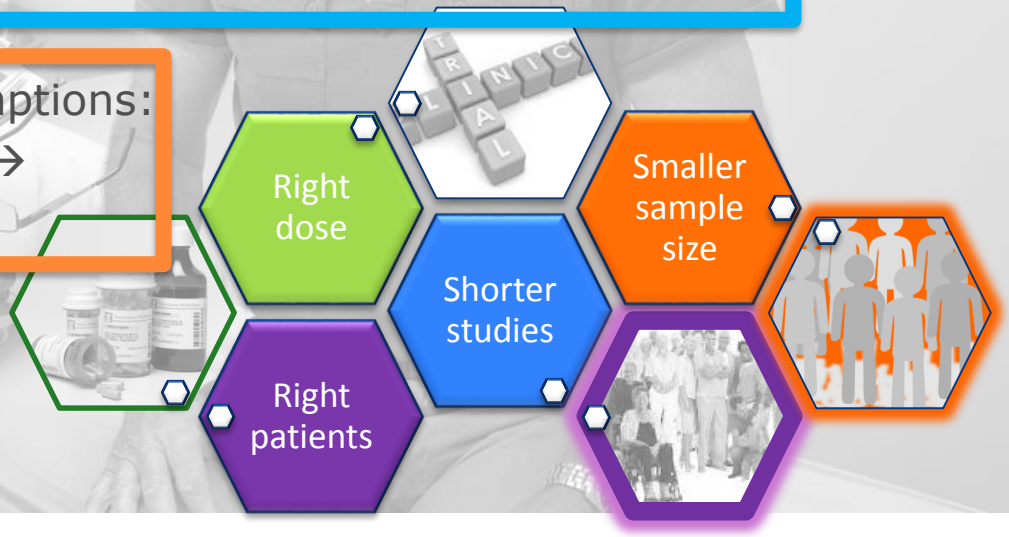
2 **ICH E20 IWG/EWG**

3 **1st Meeting at the ICH Assembly**

Background to the Proposal

Increased efficiency of ACT: To save resources and accelerate market approval by mitigating the risks associated with

- Dose(s) selection and characterization of the dose-response profile
  - Minimize exposure of patients to ineffective/toxic drugs
- Patient population identification: who benefits the most?
- Uncertainty around treatment effect: stop early for superior efficacy or futility; save resources and ethical considerations
- Uncertainty around design assumptions: treatment effect size, variability → sample size determination



Background to the Proposal

Increased productivity: To better leverage information (=data) and reduce time at each stage by

- **More efficient and informed** designed program in late development
- **Optimize treatment assignment** to populations subgroups or indications (enrichment; response adaptive randomization)
- **Combine multiple stages** into a seamless design (e.g PoC/Dose Finding)
- Better use of operational resources when combining multiple indications or compounds into a single **master protocol** (platform designs)

Increased portfolio value: to make the Correct decision, at the earliest time point, in the most efficient manner possible by:

- Enabling **better management of resources** across pipelines of products
- Maximizing the **probability of success**
- Optimizing investment **decision making**

Challenges and Opportunities

Uncertainties due to:

- Differences in current RA Guidances with regard to the terminology of adaptive designs
- The lack of common principles for the design, conduct, analysis, and interpretation of adaptive clinical trials
- The lack of common expectations for documentation to support regulatory review

Different perspectives among regulatory agencies in different regions have resulted in uncertainty in the use of adaptive clinical trials in a global environment

Opportunities:

- Harmonized perspective for ACT among the different ICH regions will allow sponsors and regulators to build an efficient multi-regional prospective plan for drug development which incorporates these innovative designs

Proposal for ICH E20 Guideline

- **Scope:** A new ICH guideline on the design, conduct, analysis, and interpretation of adaptive clinical trials
- **Objective:** To provide a transparent and harmonized set of principles for the design, conduct, analysis, and interpretation of adaptive clinical trials
- **Primary Focus:** While adaptive clinical trials throughout all stages of development are in scope, the primary focus of the guideline will be on confirmatory clinical trials

ICH E20 Informal Working Group

- The IWG should consist of ICH Members and Observers
- The expertise should be a balance of clinical and statistical experts with experience in innovative clinical trial approaches
- The ICH IWG was launched in June 2019 to finalize the Concept Paper and Business Plan prior to the formation of an ICH Expert Working Group (EWG)
- The Concept Paper and Business Plan have been approved by the ICH Assembly Meeting in Singapore on November 20, 2019
- The ICH Assembly endorsed also the creation of the E20 EWG

ICH E20 Expert Working Group

- **Rapporteur:** Z. John Zhong (PhRMA)
- **Regulatory Chair:** Gregory Levin (FDA)

- **PhRMA:** Amy Xia & Vlad Dragalin
- **EFPIA:** Bruno Flamion & Hans Ulrich Burger
- **BIO:** Frank Bretz & Erik Pulkstenis
- **JPMA:** Hideki Suganami & Masayo Miyata
- **IGBA:** Kevinkumar Kansagra
- **IFPMA:** Xiaoni Liu & Zhihong Lu

- **FDA:** John Scott
- **EC:** Armin Koch & Frank Petavy
- **MHLW/PMDA:** Yuki Ando & Naoto Kotani
- **Health Canada:** Roxana Alexa & Catherine Njue
- **Swissmedic:** Lorenzo Hess & Verena Gafner
- **ANVISA:** Carolina Pingret Cintra & Leonardo Fabio Costa Filho
- **HSA:** Lisa Tan & Tan Hui Xing
- **MFDS:** Myung Ah Chung
- **NMPA:** Jianhong Pan & Yunhong Huang

- **TFDA:** Lien-Cheng Chang & Wei-Lun Peng
- **GHC:** Turki Althunian

ICH Assembly Meeting in Singapore, Nov 17-20, 2019

Progress made at the meeting

- Reviewed regional regulatory Guidances from EC/EMA, US FDA, NMPA, and MHLW/PMDA
- Reviewed industry perspectives
- Discussed the scope of the future ICH E20 Guideline, along with some specifics on
  - Definition of adaptive clinical trials
  - What should and should not be in scope
  - Table of contents

Progress made at the meeting

- Discussed a plan to move from scope to the future guideline document
  - Writing team format
  - Consensus on a Working Plan
- Requests to the Assembly
  - Endorsement of Concept paper and Business plan
  - Endorsement to form the EWG
  - Work Plan endorsement
- All Requests have been endorsed

Exiting definitions of an adaptive design

Adaptive Design is one that uses *accumulating data from the ongoing trial* to modify aspects of the study without undermining the validity and integrity of the trial
- PhRMA ADWG (2006)

Adaptive design is defined as a clinical trial design that allows for *prospectively planned modifications* to one or more aspects of the design *based on accumulating data from subjects in the trial*
– FDA Guidance on AD (2018)

A clinical trial design that will have adaptations based on the accumulating data from the trial and/or *external data*. Modifications based on the accumulating data from the trial should be pre-specified prior to initiation of the trial
– Draft NMPA (2019)

A study design is adaptive if statistical methodology allows the modification of a design element (e.g. sample-size, randomization ratio, number of treatment arms) at an IA *with full control of the type I error*
– EMA reflection paper (2007)

Core Principles

1. Control of chance of erroneous conclusions (control of Type I error probability)
2. Reliability of estimation
3. Maintenance of trial integrity
4. Adequate trial planning

- "Design is fit-for-purpose" – *still under discussion*

Draft Structure of the Guideline

- Introduction (benefits, rationale, scenarios) and Scope
- Definitions and Concepts
- Key Principles (incl. guidance on how to achieve…)
- Adaptive Trials Landscaping/Relevance
- Special Topics/Considerations
  - DMC (or DMC alternatives in adaptive setting)
  - Statistical aspects / Bayesian adaptive designs
  - Design changes based on external data / potential surrogates
  - Safety considerations
  - Unplanned design changes based on comparative interim results
  - Secondary endpoints
  - Operational aspects
- Documentation/Interactions
- Include examples (NB. esp. training materials).

Expected future Key Milestones

Expected Completion date	Deliverables
November 2019	• Formation of E20 EWG
May 2020	• Discussion of draft E20 guideline
November 2020	• First Draft E20 guideline available for EWG review (Technical Document)
May 2021	• Ongoing discussion of draft E20 guideline
November 2021	• Step 1, Step2a and Step 2b: Draft E20 guideline endorsed
2022	• Step 3: Review of submitted comments • Develop training materials
2023	• Step 4: Finalize training materials • Step 4: Finalization of E20 guideline

Conclusions

- E20 Informal/Expert WG collaborates well together
- Progress made on the details of the scope
  - Topics needing further discussion identified
- No major barrier to harmonization identified
- Informal/Expert WG progress on-track
  - Consensus on Work Plan

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January 15, 2020

Julius Caesar Bustamante – *Pajaros*
Artwork from Healing Arts Initiative, a nonprofit organization that inspires healing, growth and learning through access to the arts for the culturally underserved.

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