ICH E9(R1): Status of addendum and comments

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EFSPI Regulatory Statistics Workshop 24th Sept 2018

International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Disclaimer (Chrissie Fletcher)

- **The views expressed herein represent those of the presenter and do not represent the views or practices of Amgen, the views of the other Industry representatives on the ICH E9 working group, or the views of the general Pharmaceutical Industry.**

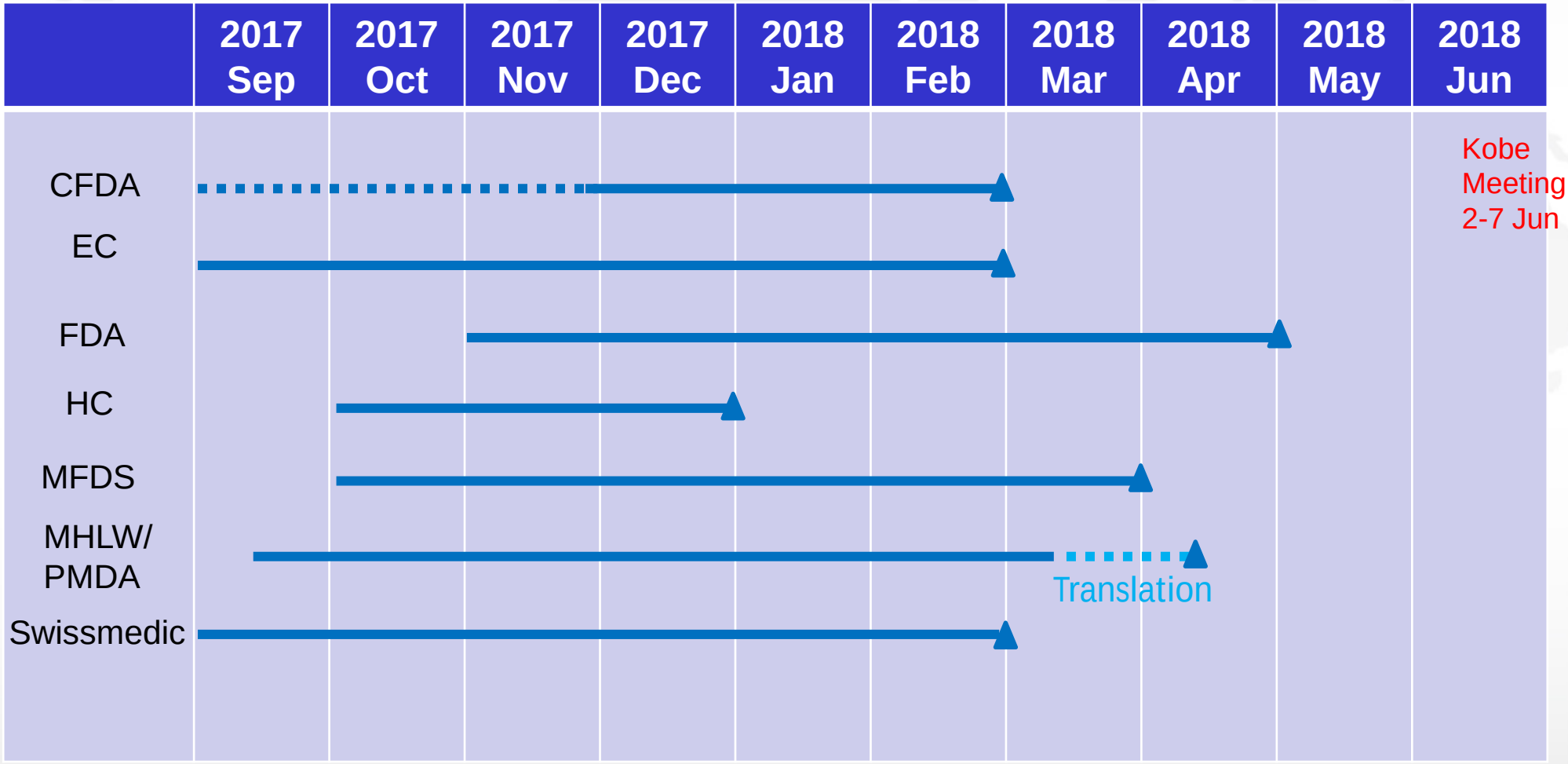
Acknowledgements

EU E9 Working Group members: Frank Bretz (Novartis), Frank Petavy (EMA), and Rob Hemmings (MHRA)

Agenda

- Pubic comments on the draft addendum
- E9(R1) timelines
- E9 WG activities
- Recent E9 Working Group (WG) achievements
- Other estimand discussions
- Conclusions

ICH E9(R1) Step 3 consultation period



Public comments on the draft addendum

- **Thanks to everyone who reviewed the draft addendum and contributed comments**
- **1200+ comments received**
  - EU - 464
  - US - 297
  - JAPAN - 203
  - CANADA - 203
  - CHINA - 59
  - TAIWAN - 17
  - BRAZIL - 5

Key themes emerging from pubic comments

- Definition of intention to treat
- Grouping estimand strategies
- Different types of intercurrent events
- Using the term “Intercurrent”
- ‘Hypothetical’ scenarios
- Main vs supplemental estimands vs sensitivity analyses
- Estimands for non-inferiority trials
- Estimands for safety
- Role of analysis sets
- Missing data versus intercurrent events

Key themes emerging from pubic comments (cont.)

- Confirmatory trials versus other trials
- Regulatory preferences
- Addendum vs E9
- More details on principal stratification
- Where to document estimands
- How much detail is needed?
- Pre-specifying estimands vs updating prior to unblinding
- Too long, duplicate text
- Make it readable for non-statisticians
- Clinical relevance

E9(R1) Timelines

- **Finalise E9 addendum at June 2019 ICH meeting**
  - No fundamental changes to concept or framework identified from reviewing public comments;
  - Followed E17 experience and allowed for 3 ICH meetings to incorporate comments

E9 WG Activities

- **Incorporating public comments**
  - Key themes from public consultation were discussed in detail in June 2018 (ICH Kobe, Japan)
    - Line by line review was pre-read
  - Authoring team are revising sections and proposing alternatives
  - Lots more discussions……
- **Finalising animation video**
- **Continue to present at scientific meetings and hold workshops**
  - Recent EFPIA workshop discussing estimands in non-inferiority trials (and estimands for safety)

Recent E9 WG Achievements

ICH harmonisation for better health

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The ICH E9(R1) Step 2 Training Material available now on the ICH website

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21 August 2018

The ICH E9(R1) Step 2 Training Material was produced by the ICH E9(R1) Expert Working Group to accompany the Draft ICH E9(R1) Addendum, and is intended to support the scientific community in the comprehension of a new framework to define estimands based on the trial objective and considering intercurrent events. The training material is accompanied by examples and case studies.

Please find on the E9(R1) page the Training Material for download.

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http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html#9-2

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Draft (Step 2) guideline ICH E9(R1)

Estimands and Sensitivity Analysis in Clinical Trials

Training module 1: Summary

Addendum to ICH E9 – Statistical Principles for Clinical Trials
ICH E9(R1) Expert Working Group
June 2018

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Estimands and Sensitivity Analysis in Clinical Trials

Training module 2.1: Introduction

Addendum to ICH E9 – Statistical Principles for Clinical Trials
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Estimands and Sensitivity Analysis in Clinical Trials

Training module 2.2 Framework

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Training module 2.3: Estimands

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Estimands and Sensitivity Analysis in Clinical Trials

Training module 2.4: Impact on trial design and conduct

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Training module 2.5: Impact on trial analysis

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Estimands and Sensitivity Analysis in Clinical Trials

Training module 2.6: Documenting estimands and sensitivity analysis

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Estimands and Sensitivity Analysis in Clinical Trials

Training module 3: Generic Example

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A thinking process…

1. Therapeutic setting and intent of treatment determine trial objective
2. Identify intercurrent events
3. Discuss strategies to address intercurrent events
4. Construct the estimand(s)
5. Align choices for trial design, data collection and method of estimation
6. Identify assumptions for the main analysis and suitable sensitivity analyses to investigate these assumptions
7. Document the chosen estimands

Other estimand discussions

- **DIA "Getting the Questions Right: Safety and Benefit-Risk Evaluation"**
  - "The ICH E9 estimand framework may be useful for benefit-risk evaluation"
  - "What is the right safety question?"
  - "Pairing efficacy and safety estimands may each require their own estimand strategies to avoid bias"
  - HTA views (IQWiG): "…use of treatment policy or composite strategies for assessing benefit, and treatment policy for safety"
- **TransCelerate**
  - Common Protocol Template and Common SAP Template

Other estimand discussions (cont.)

- **Estimands in time to event**
  - Censoring versus intercurrent events
  - Saad et al. (2018) “Understanding and Communicating Measures of Treatment Effect on Survival: Can We Do Better?”
- **Disease-area specific Industry estimand working groups**
  - E.g. oncology, neuroscience, respiratory, ..
- **Publications emerging, e.g.**
  - “Treatment Effect Quantification for Time-to-event Endpoints - Estimands, Analysis Strategies, and beyond” by Kaspar Rufibach

Conclusions

- **Substantial review of the draft addendum across all ICH regions**
- **A number of key areas of focus raised and the E9 WG are in the process of incorporating the comments**
- **The E9 WG are targeting finalising E9(R1) in June 2019**
- **Please share the ICH E9(R1) training slides within your institutions cross-functionally and within your Industry/Professional associations**