ICH E9 addendum: Key themes raised during public consultation

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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

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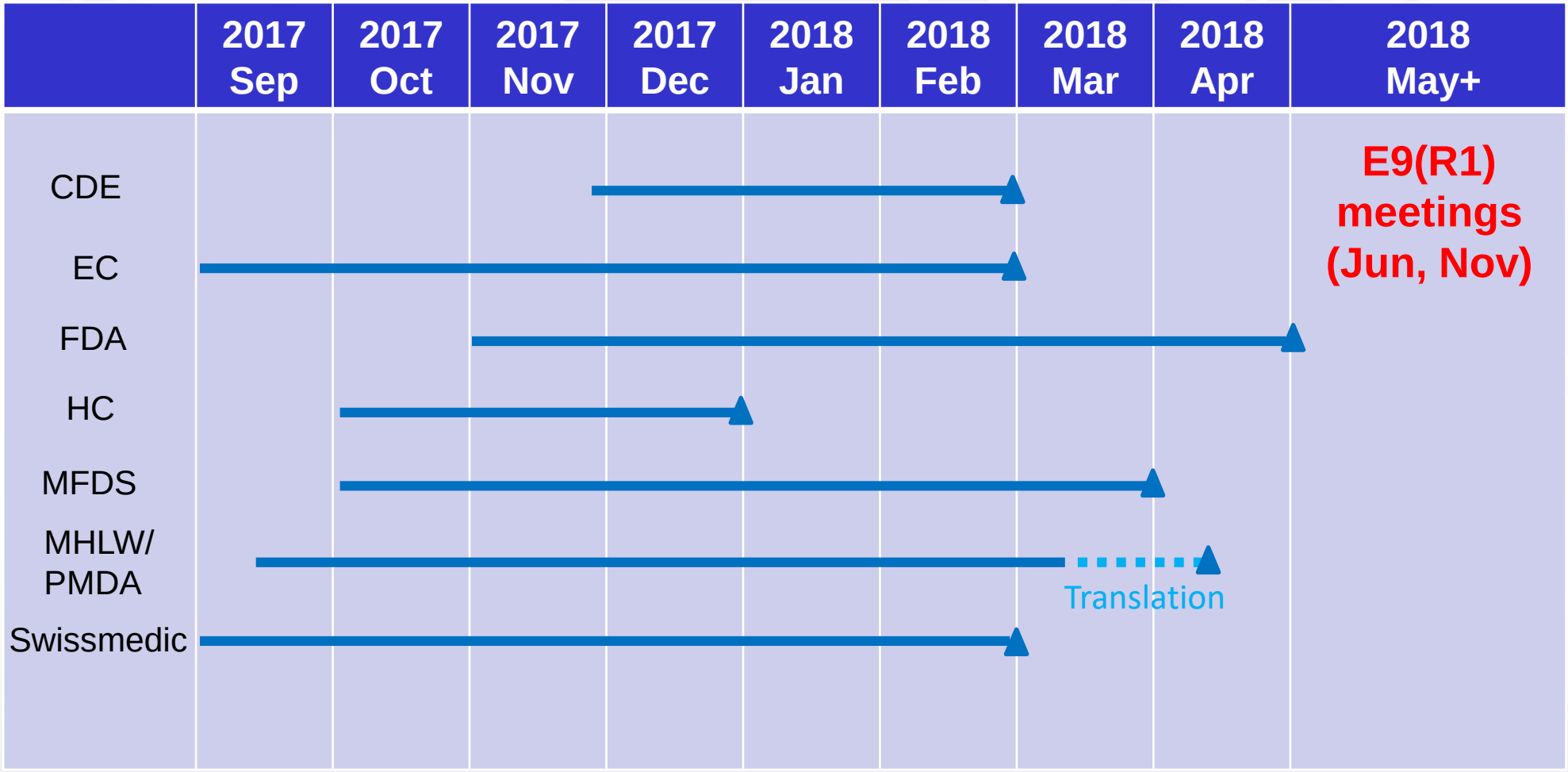
Agenda

- **Key themes emerging from the public comments on the draft addendum**
- **E9(R1) timelines**
- **E9 WG activities**
- **Recent E9 Working Group (WG) achievements**
- **Other estimand discussions**
- **Conclusions**

ICH E9(R1) consultation period finished



Public comments on the draft addendum

- **Thanks to everyone who reviewed the draft addendum and contributed comments**
- **More than 1000 comments received**
  - Comments received from all major regions, in decreasing order: Europe, U.S.A., Japan, Canada, China, Taiwan, Brazil

Key themes emerging from public comments

- Definition of intention to treat
- Grouping estimand strategies
- Composite strategy aligned to treatment policy
- More details on principal stratification
- Does PS align to clinical practice?
- ‘Hypothetical’ scenarios
- Different types of intercurrent events
- Using the term “Intercurrent”
- IEs versus IPDs
- Missing data versus intercurrent events
- Study design as an estimand attribute

Key themes emerging from public comments (cont.)

- Main estimands vs supplemental estimands vs sensitivity analyses
- Estimands for non-inferiority trials
- Estimands for safety
- Estimands for benefit-risk
- Estimands in adaptive trials
- Where to document estimands
- How much detail is needed?
- Pre-specifying estimands vs updating prior to unblinding
- PICOS (HTA) vs estimand attributes
- Describing estimands in product labels

Key themes emerging from public comments (cont.)

- Methodological challenges in applying specific strategies
- Graphics to illustrate relative positioning of estimands
- Statistical significance in sensitivity analyses
- Impact to sample size
- Sensitivity analyses for subgroups
- What to do if meaningful value does not exist, e.g. death
- Truly missing outcome data
- Role of baseline covariates

Key themes emerging from public comments (cont.)

- Confirmatory trials versus other trials
- Regulatory preferences
- Addendum vs E9
- Role of analysis sets
- Per-protocol analyses
- E17 and regional considerations
- Considerations of different stakeholders
- Addendum too long, duplicate text
- Make it readable for non-statisticians
- Clinical relevance
- Case studies
- Expand glossary

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 and Nov 2018 (ICH Kobe, Japan & Charlotte, USA)
    - Line by line review
  - Authoring team are revising sections and proposing alternatives
  - Lots more discussions……
- **Finalising animation video**
- **Continue to present at scientific meetings and hold workshops**
  - EFPIA/EFSPI workshop Sept 2018 discussing estimands in non-inferiority trials (and estimands for safety)

Recent E9 WG Achievements

~200 training slides

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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 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

A thinking process…

1. Therapeutic setting and intent of treatment determining a trial objective
2. Identify intercurrent events
3. Discuss strategies to address intercurrent events
4. Construct the estimand(s)
5. Align choices on 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 (CSAP)

CSAP template – caution!

Objective Clinical Category	Statistical Category	Estimand[1] Variable/ Endpoint	Population	IES[1]	PLS[1] (Analysis)
Primary Objective: <Efficacy objective as written in protocol, e.g., to compare the efficacy/demonstrate superiority of <study intervention> with placebo/active control in participants with <indication> with respect to:					
Efficacy Category 1	Primary/MCP	Change from baseline in <clinical variable 1> <at timepoint>	FA	Initiation of rescue medication: "had rescue medication not been initiated" (hypothetical) Discontinuation of treatment due to adverse event (AE):	Mean difference between interventions (LSMD from CFB ANCOVA with MI from participants from same randomized arm off-treatment at <timepoint>)
	Sensitivity (<alternate assumptions>)				(LSMD from CFB ANCOVA with reference-based MI)
	Supplementary	<clinical variable 1> responder (criterion) and rescue medication not initiated <at timepoint> and remained adherent to intervention	FAS	Captured in variable definition (composite)	Odds ratio between interventions (Logistic regression)
	Secondary/MCP		FAS		

Population = target population not analysis set

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**

Estimand = A Mindset (anagram)

- **Fundamentally change the way how we plan and design clinical trials**
- **Mutual understanding between clinicians and statisticians is crucial**
- **Established statistical approaches may need to be challenged**
  - No one-size-fits-all estimands are available (or even desirable)
  - Focus on causal estimands, hence the need to embrace “new” methodologies (e.g. causal inference)
    - What to do with established approaches that do not provide causal treatment effects (e.g. hazard ratios)?