Overview of ICH E9 (R1)

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E9 and E9(R1)

- Nov 1998: ICH-E9 “Statistical Principles for Clinical Trials” was issued in Japan.
- 2013: Proposal of E9(R1) by EU
- Jun 2014: Approval of the establishment of EWG
- Aug - Oct 2014: Nomination of EWG, Approval of the Concept Paper
  - “Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials”
- Nov 2014: 1st face-to-face meeting in Lisbon
- Jun 2015: 2nd face-to-face meeting in Fukuoka
- Dec 2015: 3rd face-to-face meeting in Jacksonville

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Members of EWG

EU	Robert Hemmings*, Frank Petavy
EFPIA	Christine Fletcher (Amgen), Frank Bretz (Novartis)
MHLW / PMDA	Yuki Ando, Ayako Hara, Hirofumi Minami
JPMA	Satoru Tsuchiya (Sumitomo Dainippon), Satoru Fukinbara (Ono), Hideki Suganami (Kowa)
FDA	Estelle Russek-Cohen**, Tom Permutt
PhRMA	Devan Mehrotra (Merck), Vladamir Dragalin (J & J)
Health Canada	Catherine Njue
DoH of Chinese Taipei	Mey Wang
DRA of Brazil	Leonardo Fabio Costa Filho,

*: Rapporteur, **: Regulatory Chair

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Outline

- E9 addendum but new topic for improved clinical trial planning, conduct, analysis and interpretation.
- Problem statements:
  - ‘Estimand’: Need to clarify what measure of treatment effect is being estimated in a clinical trial. Failure to do so results in misalignment between trial objectives, conduct, analysis and confusion in interpretation.
  - ‘Sensitivity analysis’: Current practice can lead to uninformative analyses and mis-direction and confusion for decision makers.

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Outline

- Scope: This document presents a structured framework to bridge trial objectives with proper inference tools, permitting more coherent inference and decision making. The focus is on the principles that allow defining an estimand and a structure for identifying sensitivity analyses.

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Explaining the ‘estimand’

- The key message is the importance of clearly formulating and articulating, in order, the trial objectives, estimand, informing design and analysis.
- Confusion in regulatory submissions has arisen, in part, due to this order being essentially reversed in practice, with the estimand being implicitly defined as a consequence of the trial design and statistical analysis methodology.
- This is not hypothetical! Dapagliflozin (US FDA Advisory Committee, 2011), Bronchitol… ≈10 examples shared in Fukuoka.

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Dapagliflozin – for illustration

- Primary endpoint: Change in HbA1c from baseline to 24 weeks
- Analysis set: modified intention to treat
- Sponsor proposal: Data after initiation of rescue medication was excluded from the analysis.
- FDA reviewer: *"While FDA has implicitly endorsed LOCF imputation for diabetes trials in the past, there is now more awareness in the statistical community of the limitations of this approach. Instead I have included a sensitivity analysis in which the primary HbA1c outcomes are used regardless of rescue treatment, and no statistical adjustment is made for rescue. This approach is also imperfect, but it comes closer to being a true intent-to-treat (ITT) analysis because it disregards the non-randomized rescue treatment."*

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Dapagliflozin – for illustration

Different perspectives on the inclusion of data

- Sponsor: Remove data after initiation of rescue medication
- FDA: Include all data regardless of initiation of rescue medication

Implied ‘scientific questions of interest’:

- Sponsor: Attempt to establish the treatment effect of the initially randomized treatments had no patient received rescue medication
- FDA: Compare treatment policies ‘dapagliflozin plus rescue’ versus ‘control plus rescue’

Disagreement over which property to estimate – the estimand.

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EWG Objective

- Improved framework for clinical trial planning, conduct, analysis and interpretation.
  - Trial Objective
  - (Consequent) Estimand
  - (Choice of) Trial design and analysis methodology
  - (Consequent) Sensitivity analyses
- Current practice is often not aligned with this proposed framework.

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Defining the ‘estimand’

- Generally, an estimand reflects what is to be estimated to address the scientific question of interest posed by a clinical trial. The choice of an estimand involves three attributes:
  - Population,
  - Endpoint, and
  - Measure of intervention effect.

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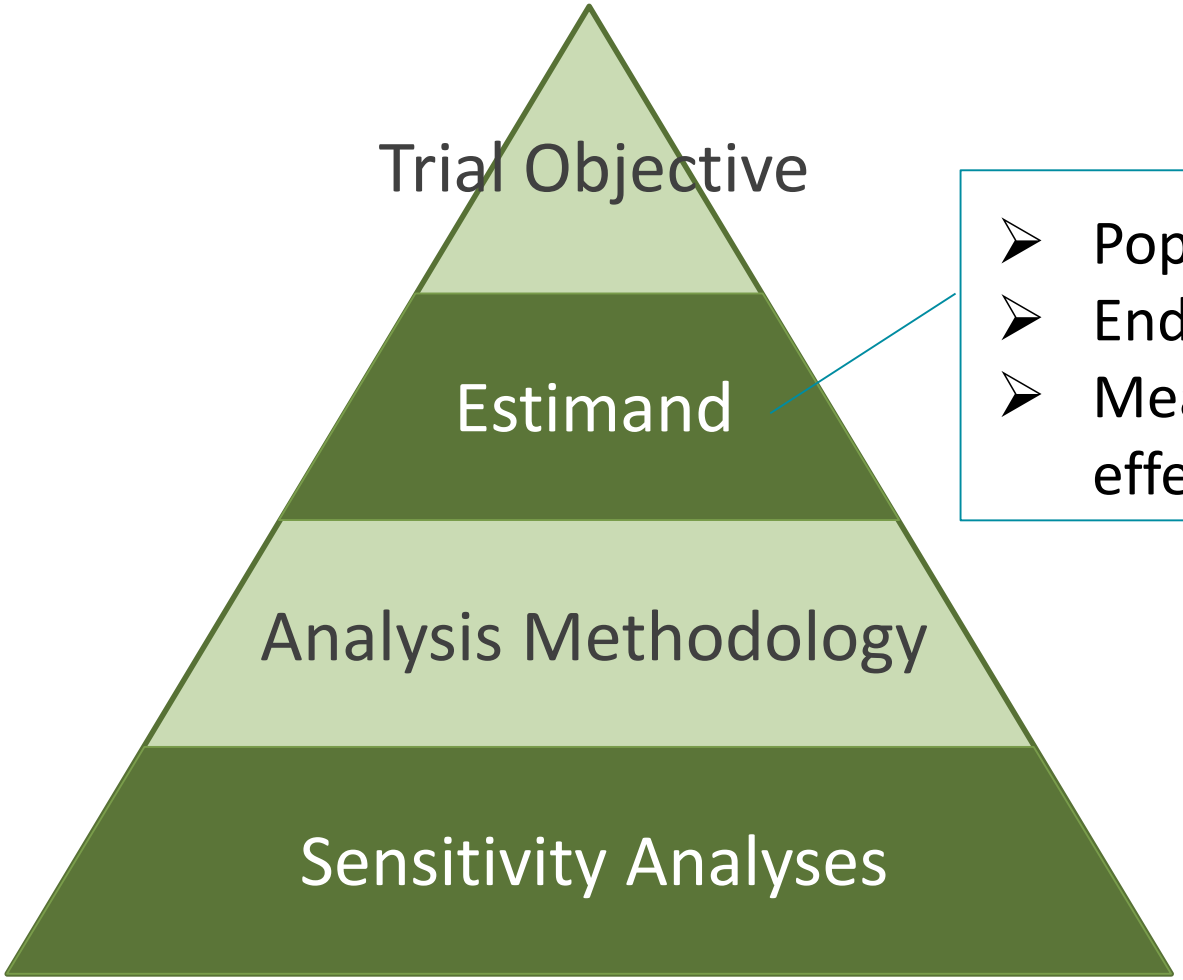
Framework under discussion



- Population
- Endpoint
- Measure of intervention effect

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Sensitivity analyses

- Current practice is to present a multitude of analyses, P-values, estimated effects etc. without particular rationale or structure.
- Aim for a targeted investigation of robustness to potential problems - important data limitations, assumptions and analytic approaches - the robustness of the estimate in respect of a particular estimand.
- In addition, rather than to present a series of P-values etc. that compete for the attention of decision makers, change the focus to describe the extent to which a problem must be present in order to challenge the result of the primary analysis.

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Survey of ‘baseline’

- Current situation of estimands and sensitivity analyses in several therapeutic areas
  - “Quantifying the impact of a new framework on clinical operations”
- Circulated to the statisticians who belong to industry, regulatory agencies and academia in May 2015
  - In Japan, JPMA, PMDA, and The Biometric Society of Japan
  - N=1258+

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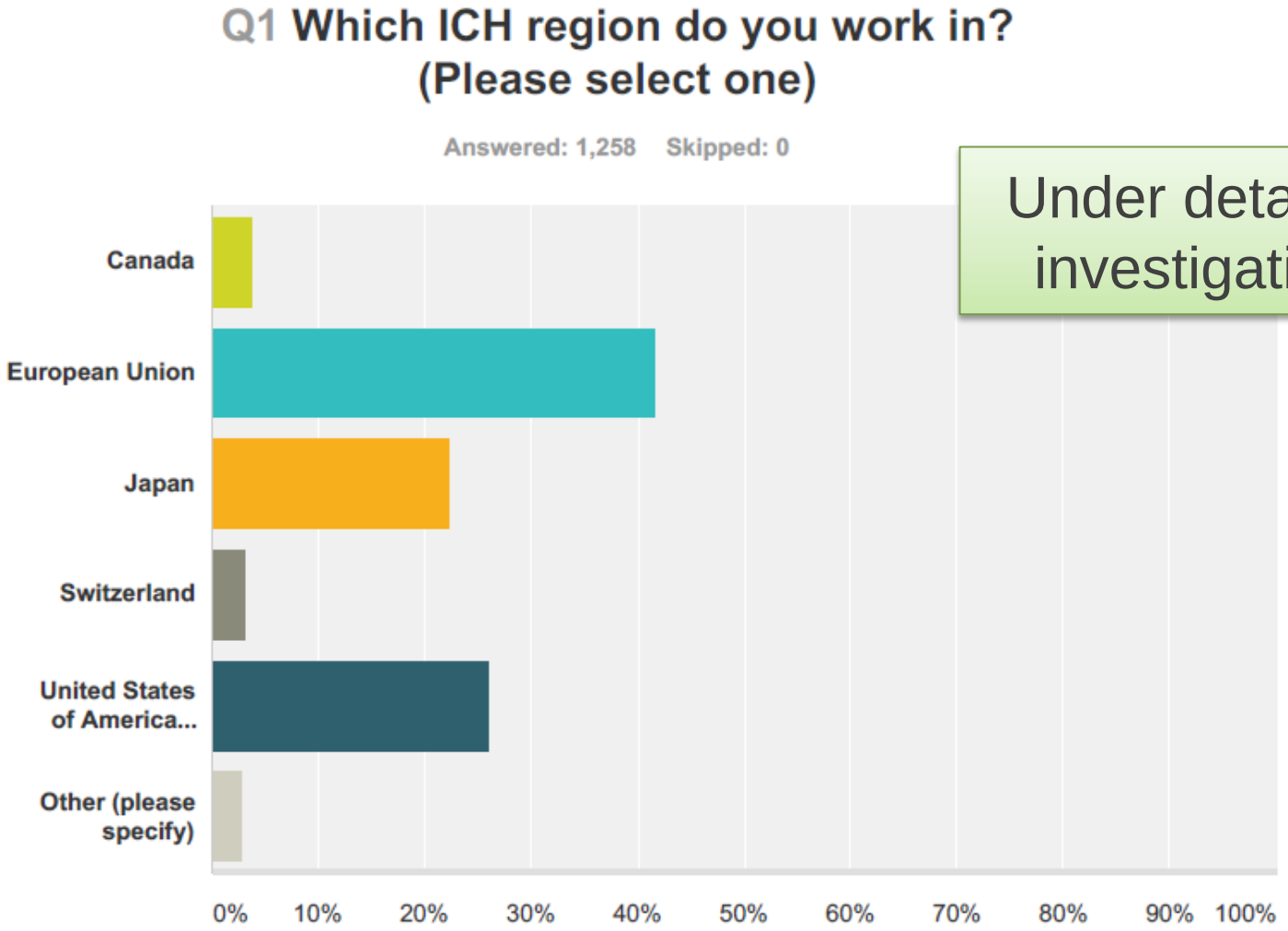
Survey of ‘baseline’



Under detailed investigation

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Tasks

- (Informal discussion with clinical colleagues etc. with using the lay summary / case studies)
- Technical Document
  - Main text of addendum
- Appendix
  - Technical details

- Preparation for the next face-to-face meeting in Jacksonville in Dec 2015
  - Monthly teleconference for the discussion on the definition, case studies, and technical details

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Experiences in PMDA

- Limited experiences in consultation meetings
- Original question was “What is different from the past situation?”, but the reviewers understood the elements of the estimand that had been usually discussed.
- Reviewers may have different view on the different drugs for the same disease.
- Possible confusion caused by terminology
  - “ITT estimand”, “Effectiveness estimand” ?
  - ITT … concept? name of estimand? or analysis set?

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Current views

- What to expect from E9(R1)?
  - Framework of choice of estimand and sensitivity analysis, as addendum of “E9: Statistical Principles for Clinical Trials”
  - Clear description of the relationship to the contents in original E9
  - Not to expect strong recommendation of particular estimand/ analysis method
- Each element of estimand is not new for us.
- The important point is choosing appropriate estimand with consideration for
  - Therapeutic area
  - Characteristics of the drug
  - Alternative therapies
  - etc,

  and keeping good balance of what we should investigate and the environment of the trial.

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Ask