Draft ICH Guidance on Estimands and Sensitivity Analyses: Why and What?

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Acknowledgement: ICH E9/R1 Expert Working Group

Conference on Statistical Issues in Clinical Trials

University of Pennsylvania

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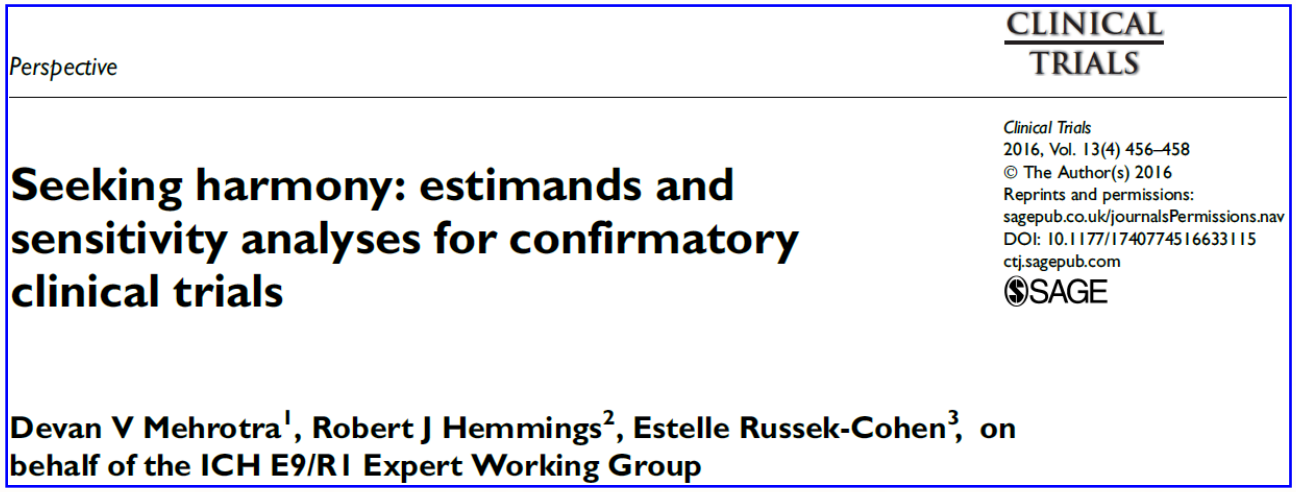
Background

- ICH = International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
- ICH E9 (Statistical Principles for Clinical Trials; 1995)
  - Articulated foundational principles (randomization, double blind, interim analysis, non-inferiority, etc.)
  - Has served as a bedrock of regulatory guidance on major statistical aspects of confirmatory clinical trials
- 2013-14: regulatory statisticians proposed creation of an expert working group (EWG) to develop an E9 addendum (E9/R1) on **estimands** and **sensitivity analyses**
- Since Nov 2014, EWG (regulatory & industry statisticians) has met every 6 months and conducted monthly telecons

Background [2]

- 3-4Q 2017: E9/R1 draft was released for public comment across all the ICH regions (some review periods still open)
- The purpose of today's presentation is to address:
  - **Why** was E9/R1 deemed necessary?
  - **What** is in the draft E9/R1?

ICH E9/R1 concept paper (www.ich.org)



Perspective

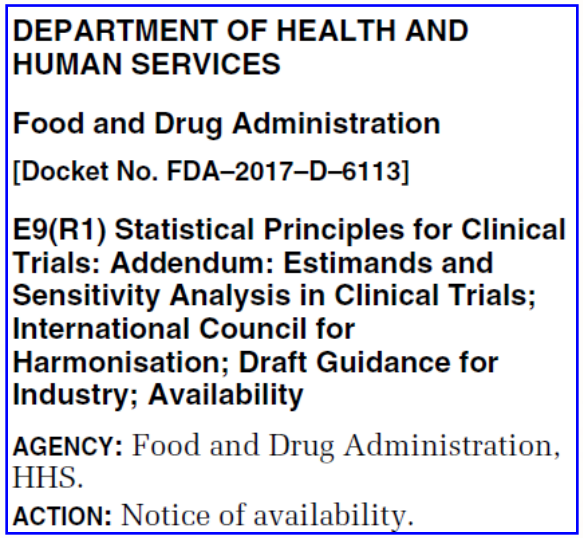
CLINICAL TRIALS

Seeking harmony: estimands and sensitivity analyses for confirmatory clinical trials

Clinical Trials
2016, Vol. 13(4) 456–458

DOI: 10.1177/1740774516633115
ctj.sagepub.com
SAGE

Devan V Mehrotra[1], Robert J Hemmings[2], Estelle Russek-Cohen[3], on behalf of the ICH E9/R1 Expert Working Group



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2017–D–6113]

E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials; International Council for Harmonisation; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

ICH E9/R1: Why?

Motivating Example

- Double-blind, randomized clinical trial, experimental anti-diabetic drug (treatment A) vs. placebo (treatment B)

  Endpoint = HbA1c change from baseline after 24 weeks

  Objective: estimate the between-treatment difference in population endpoint means ($\delta=\mu_A-\mu_B$) and test $H_{null}:\delta=0$

- IMPORTANT
  - Some patients will be unable to continue on assigned treatment due to intolerable side effects and/or experience inefficacy of assigned treatment
  - Either reason may necessitate switching to or adding rescue medication to try and lower HbA1c

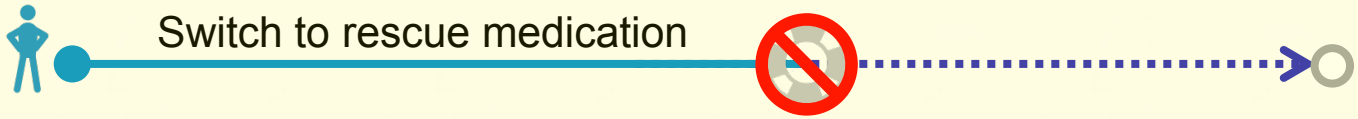
Endpoint/objective: is clinical question of interest clear? **No**

Motivating Example [2]

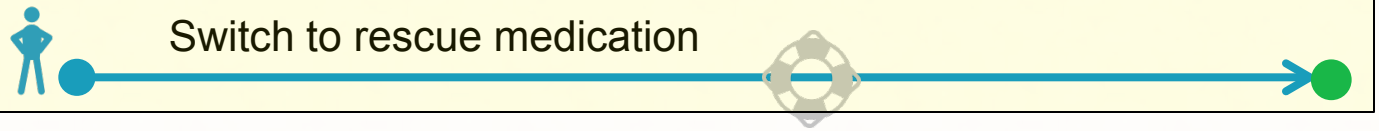
- What is the **treatment effect of interest**?
  - Combined effect of the assigned treatment and (potential) rescue medication?
  - Effect of assigned treatment only, i.e., without adding or switching to rescue medication if the assigned treatment has inefficacy or intolerability?
  - Something else?

2011 FDA advisory committee for dapagliflozin

- **Company:** Remove data after initiation of rescue medication

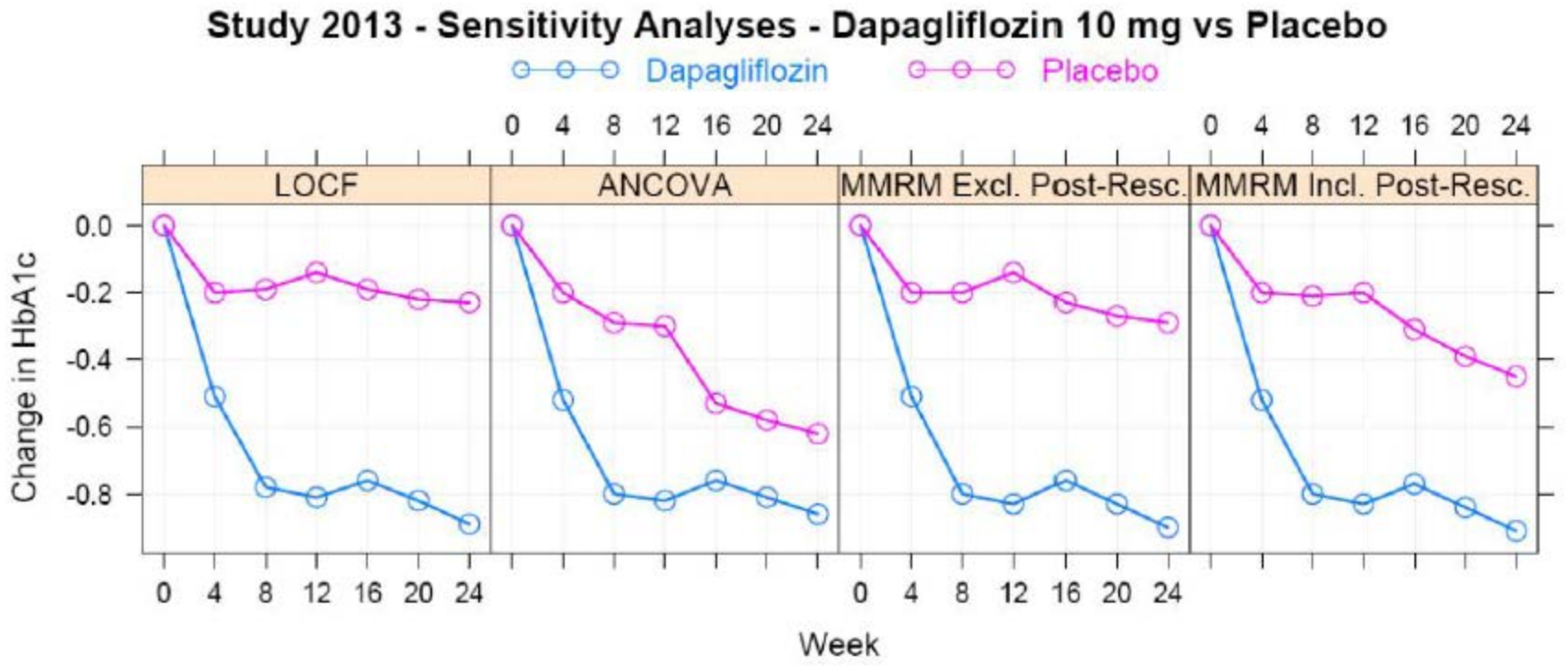


- **FDA:** Include all data regardless of rescue medication



Motivating Example [3]

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov



- What is the **treatment effect of interest**?
- Is this really a "sensitivity" analysis? **No**

E9/R1: Why was it deemed necessary?

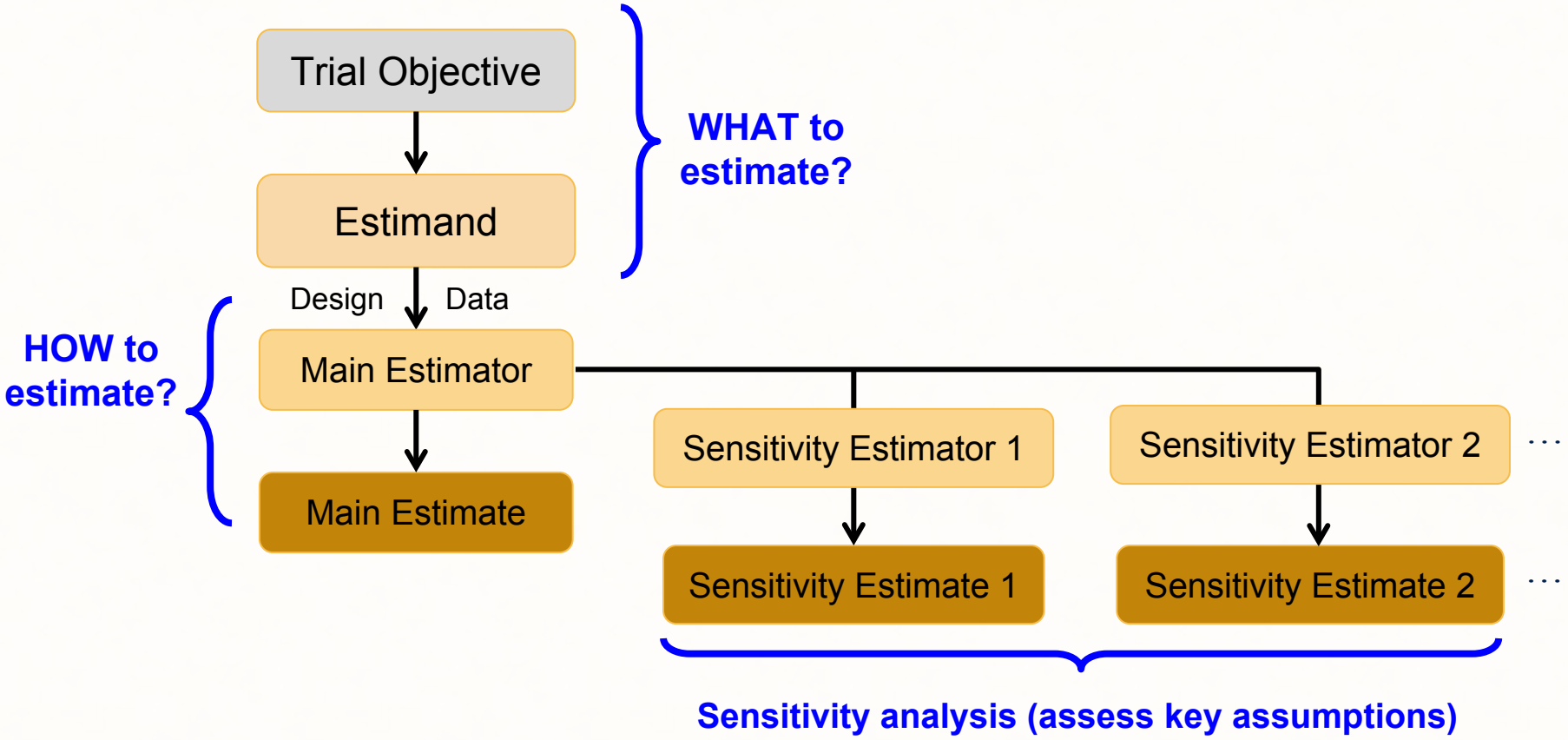
- **Comments from regulatory statisticians** on several clinical trial protocols & new drug applications (NDAs):
  - Insufficient clarity in objectives and related treatment effect parameters (i.e., estimands) of interest
  - Lack of logical connectivity between trial objectives, design, conduct, analysis and interpretation
  - Misalignment between "missing data" analysis methods and estimands of interest
  - Misunderstanding of the term "sensitivity analysis"

E9/R1 is intended to address these gaps, with a goal of improving clinical trial design/analysis/interpretation, NDA submissions and (ultimately) product labels

ICH E9/R1: What?

A Structured Framework

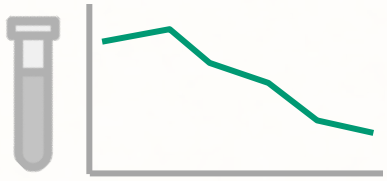
For a given trial objective: aligning target of estimation, design, method of estimation and sensitivity analysis



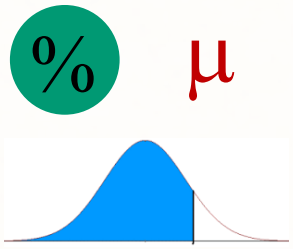
Inputs for Defining an Estimand

A
Population

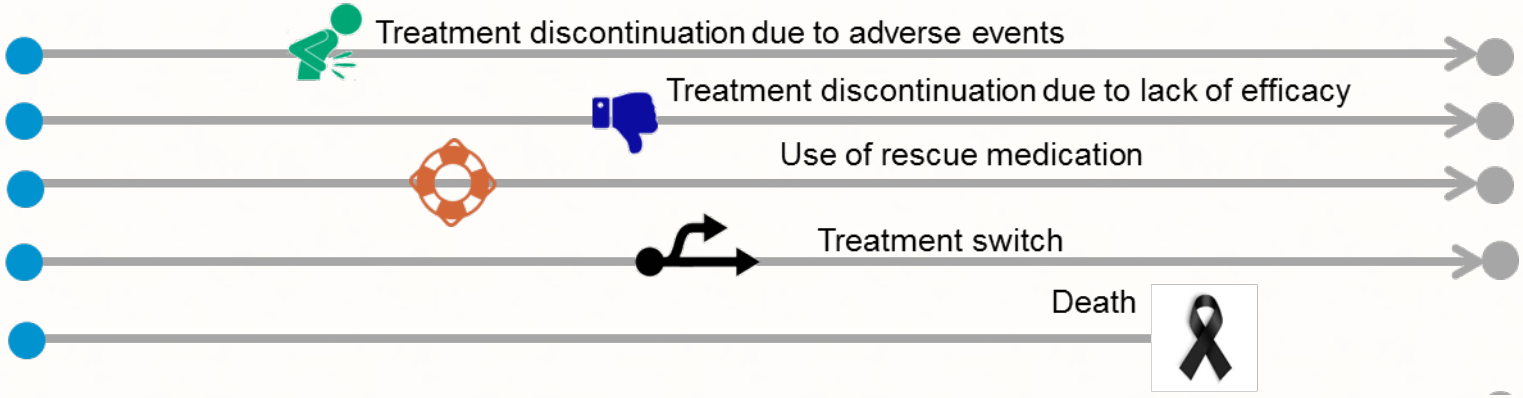
B
Variable (Endpoint)



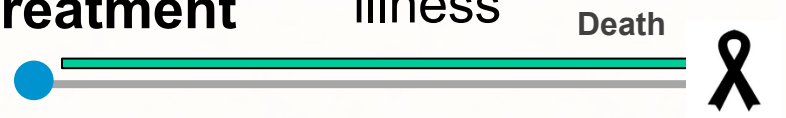
D
Population-level Endpoint Summary



C
Intercurrent Event(s)



Strategies for Addressing Intercurrent Events in the Scientific Question of Interest

Strategy	*Example of Endpoint or Effect of Interest*
Treatment Policy	Overall survival regardless of whether or when **treatment switching** happens 
Composite	Heart attack **or** **treatment discontinuation due to AE** 
Hypothetical	Change in HbA1c if **rescue medication** is not used 
Principal Stratum	Infection severity in subpopulation that will **become infected** despite preventive treatment 
While on Treatment	QoL under palliative treatment until **death** in terminal illness 

Case Study: Diabetes

- Double-blind, randomized clinical trial, drug vs. placebo

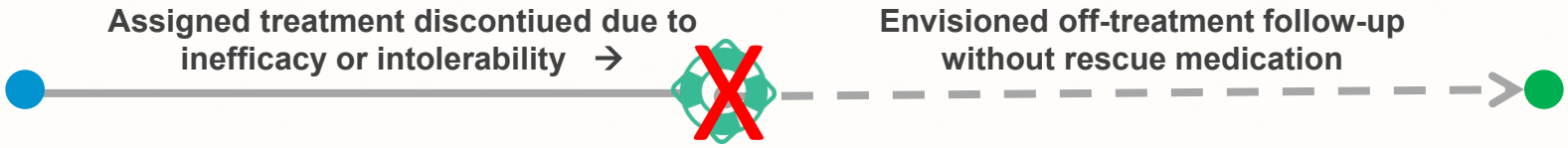
Primary Objective: assess whether drug is more effective than placebo in lowering HbA1c without rescue medication (the latter was allowed, but to address a different objective)

Construction of Primary Estimand

Population: adults with type II diabetes (per intended label)

Endpoint: HbA1c change from baseline at 24 weeks

Intercurrent event: treatment effect of interest is based on the endpoint envisioned under hypothetical scenario of no rescue medication if assigned treatment has inefficacy/intolerability

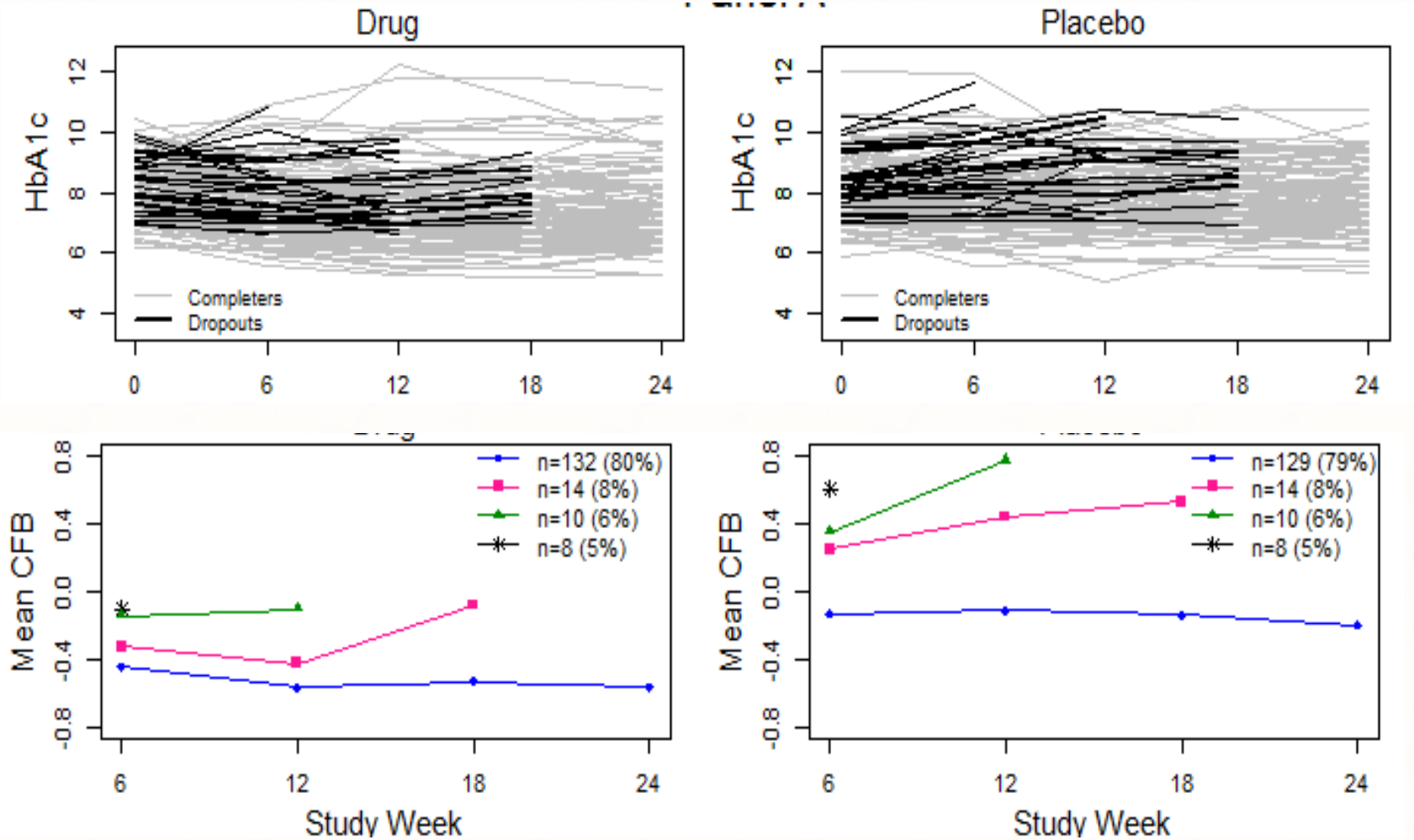


Population-level summary: mean of the endpoint

Case Study [2]

- **Estimand**: between-treatment difference in target population endpoint means for the treatment effect of interest (δ)
- **Statistical objectives**
  - Deliver acceptable point estimate and 95% CI for δ
  - Test H_{null}: $\delta=0$ vs. H_{alt}: $\delta<0$ (with type 1 error rate $\leq \alpha$)
- **Tackling rescue medication in the analysis**
  - Given estimand of interest, HbA1c values after initiation of rescue medication can be discarded, resulting in "missing" endpoint data for such patients (and dropouts)
- **Analysis challenge**: all patients need to be included in the analysis (per the estimand), so how do we tackle the missing endpoint data problem?

Case Study [3]



% missing endpoint: **20%** (33/165) Drug **21%** (34/164) Placebo

1 patient assigned to drug and 2 patients assigned to placebo were dropouts before week 6

Case Study [4]

Important: **control-based mean imputation** approach below is one of several options that can be considered in the (pre-specified) SAP

- Obs = endpoint observed, miss = endpoint missing
- π_i^{miss} = true Pr(endpoint missing under trt i) = $1 - \pi_i^{obs}$

Placebo	***Drug***
$\mu_P = \pi_P^{obs}\,\mu_P^{obs} + \pi_P^{miss}\,\mu_P^{miss}$	$\mu_D = \pi_D^{obs}\,\mu_D^{obs} + \pi_D^{miss}\,\mu_D^{miss}$
$\hat{\mu}_P = \hat{\pi}_P^{obs}\,\hat{\mu}_P^{obs} + \hat{\pi}_P^{miss}\,\hat{\mu}_P^{miss}$	$\hat{\mu}_D[c] = \hat{\pi}_D^{obs}\,\hat{\mu}_D^{obs} + \hat{\pi}_D^{miss}\,(\boldsymbol{\hat{\mu}_P + c})$

$\hat{\mu}_P^{miss}$ = estimate of μ_P assuming missing endpoints are MAR for placebo

Estimand: $\delta = \mu_D - \mu_P$

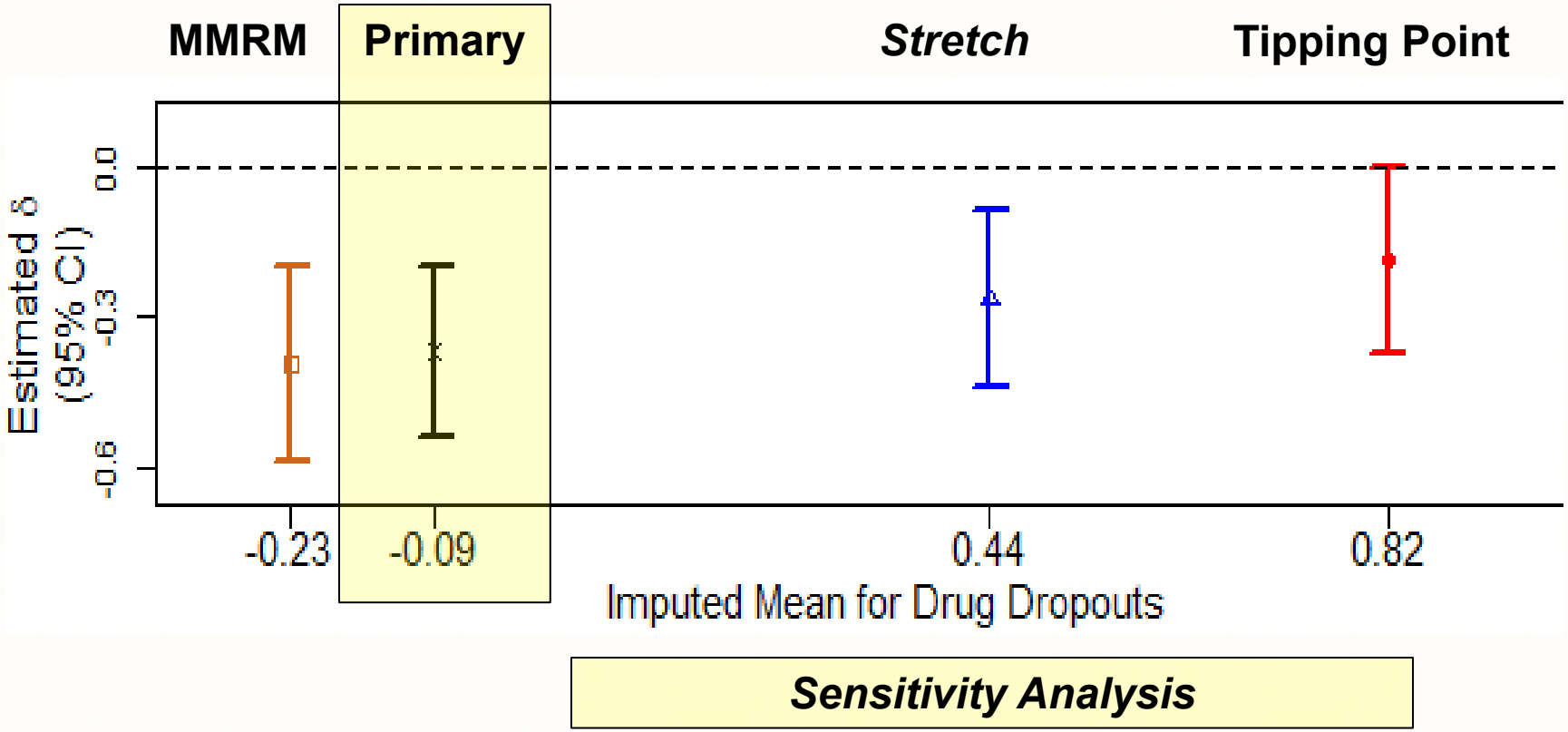
Estimation: $\hat{\delta}[c] = \hat{\mu}_D[c] - \hat{\mu}_P$

Primary Analysis: use $c = 0$

***Sensitivity Analysis*:** increase c until **Tipping Point**

Details: Mehrotra, Liu, Permutt (2017; Pharm Stat)

Case Study [5]



- MMRM: mixed model repeated measures assuming MAR dropout for drug and placebo [shown for historical reference only]
- *Stretch*: imputed mean for drug dropouts matches estimated mean for placebo dropouts assuming MAR dropout for placebo
- ***Note***: tipping point after *stretch* imputation ⇒ **robust** evidence of trtmt effect

Wrap Up

- The framework proposed in ICH E9/R1 is expected to:
  - Enable better planning and preparation of application dossiers for new drugs/vaccines/biologics
  - Strengthen understanding of decision-making by regulatory authorities and advisory committees

- The ICH E9/R1 expert working group:
  - Will begin to review/address collated public comments on the E9/R1 draft in June 2018 (Kobe, Japan)
  - Is developing a training slide deck to augment the E9/R1 text document; will include other case studies